THE NEUROPSYCHOLOGY OF MEMORY IN EARLY ALZHEIMER'S DISEASE - A LONGITUDINAL STUDY

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Publications arising from this thesis

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Greene, J.D.W., Hodges, J.R. Identification of Famous Faces and Famous Names in early Alzheimer's disease: Relationship to anterograde episodic and general semantic memory. Brain, in press

Greene, J.D.W., Hodges, J.R., Baddeley, A.D. Autobiographical memory and executive function in early dementia of Alzheimer type. Neuropsychologia, in press

Greene, J.D.W., Baddeley, A.D., Hodges, J.R. Recall and recognition of verbal and nonverbal material in early Alzheimer's disease: Applications of the Doors and People Test. Neuropsychologia, in press

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Greene, J.D.W., Hodges, J.R. A longitudinal study of the neuropsychology of memory in dementia of Alzheimer type. In preparation

Published abstracts

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Related publications

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Summary

It is well established that memory impairment is almost always the first aspect of cognition to become impaired in dementia of Alzheimer type (DAT). It has become apparent, however, that memory itself comprises various subcomponents. The nature of the memory deficit in DAT, in terms of the order in which these components of memory become impaired, and the underlying cause of these impairments, have become a focus of cognitive neuropsychological research. The ability to study patients with breakdown in multiple components of memory also offers the opportunity to expand our knowledge of the inter-relationship of these cognitive domains.

To study these questions, I administered a battery of neuropsychological tests, comprising tests of working memory, anterograde episodic memory, autobiographical memory, remote memory and semantic memory, to 33 DAT patients designated minimal (MMSE 24-30; n=17) and mild (MMSE 17-23; n=16) and 30 age-matched controls.

Firstly, a cognitive analysis was applied to the results from the famous face and famous names tests, as discussed in Chapter 3. In addition to confirming that patients, even very early in the course of DAT, show significant deficits in remote memory of this type with a mild temporal gradient, I found that the major deficit was impaired semantic knowledge regarding the famous person rather than breakdown at the pre- and post-semantic levels of face (or name) processing. There was no association between performance on anterograde and retrograde tasks, and the relationship between person-specific knowledge and semantic memory was poor. Moreover, knowledge of famous people accessed by face or by name appears to draw on the same pool of semantic information.

Naming without semantics is currently a controversial topic, with claims that it is possible to bypass semantics, and name an object (and by analogy, a known face) without having semantic identifying information about the object. In Chapter 4, I investigated this question and found no instances of ability to name a famous face without being able to identify the famous person. This argues strongly against the concept of naming without semantics.

Executive function and autobiographical memory have been shown to be impaired in established DAT. It is less clear, however, at what stage in the illness this becomes evident. In Chapter 5, I establish that while autobiographical memory is impaired even in minimal DAT, executive dysfunction only becomes apparent in mild DAT. The theoretical issue of the role of executive function in the retrieval of autobiographical memory is currently debated. I addressed this by administering a

range of tests of both executive function and autobiographical memory to the DAT patients and controls. It appears that impairment of executive function plays a limited role in the autobiographical memory deficit in DAT.

Although it is well established that episodic memory is almost always the first aspect of memory to become impaired in DAT, the nature of this episodic disorder has not been totally resolved. For instance, there is debate regarding the relative importance of encoding, storage and retrieval deficits in DAT, and whether forgetting is normal or accelerated. In Chapter 6, I confirmed that the major impairment in anterograde memory in DAT is due to poor encoding, rather than storage or retrieval deficits. The issue of the forgetting rate in DAT is controversial. Although most studies claim that forgetting is greater in DAT, my data shows that this is largely artefactual due to the fact that short-term memory (STM) contributes to immediate but not delayed recall. Once the contribution of STM is allowed for, I found that the forgetting rate is normal. I also found limited evidence of material-specificity in the minimally affected DAT patients, suggesting that the pathology in early DAT is only occasionally asymmetrical or even unilateral.

Given the lack of a diagnostic "gold standard" for diagnosing DAT *in vivo*, various means of investigation are used to aid in the diagnosis. A practical issue relates to the relative merits of neuropsychology and SPECT imaging in the diagnosis and staging of DAT. I studied the use of functional imaging by SPECT (single photon emission computed tomography) in 31 of the above 33 DAT patients, and in 24 controls. The results confirm that different measures of memory are very useful for diagnosis and staging; SPECT was, by contrast, of more limited use. The classical pattern of regional cerebral blood flow (rCBF) changes in DAT is of initial temporo-parietal hypoperfusion, leading to more global hypoperfusion. Recently, it has been claimed that the pattern of rCBF may be more heterogeneous. In Chapter 7, I present data which show heterogeneity in the pattern of rCBF in DAT.

The aforementioned chapters relate to the cross-sectional neuropsychological and SPECT studies of DAT. Longitudinal studies are, however, recognised to be more sound methodologically than cross-sectional studies, particularly for staging DAT. I therefore extended the study by administering the same battery of tests to 24 of the original 33 DAT patients one year later, as described in Chapter 8. This gives a clearer picture of the order in which subcomponents of memory deteriorate in DAT. Analysis of group data showed that, while delayed recall of new information is the memory measure of most use in diagnosis, tests of immediate recall, remote memory and semantic memory were of more use in staging disease. Analysis of individual cases, however, again highlighted the heterogeneity in the rate of deterioration of

components of memory in individual patients, even when of the same initial dementia severity.

Cross-sectional studies of remote memory are bedevilled by lack of certainty regarding the subject's premorbid knowledge base. Longitudinal studies are particularly helpful in this instance, as the patients can act as their own controls. In Chapter 9, I found that the deterioration in face and name identification over one year was due primarily to loss of identifying information, while face naming impairment was due primarily to a variable retrieval impairment. I found that while memory for public figures deteriorated over one year, there was no such deterioration in autobiographical memory. This further supports the assertion that remote memory may be fractionated into autobiographical memory, and memory for public figures.

My contribution to this thesis

I performed the research comprising this thesis whilst employed as Research Registrar in Neurology in the University of Cambridge Neurology unit from April 1993 to September 1995.

My personal contribution to this study was as follows:

1. I designed and initiated all parts of the study.

2. I developed the battery of tests used in the neuropsychological part of the study. Some of the tests employed are in routine clinical usage. However, for the purpose of the study I specifically designed one test of remote memory (the Famous Names Test) and adapted three other tests (Autobiographical fluency, Famous Faces Test, Autobiographical Memory Interview).

3. I administered the battery of neuropsychological tests to 33 patients and 30 controls, and readministered the tests to 24 of the patients and 5 of the controls after an interval of approximately twelve months.

4. I analysed quantitatively the SPECT scans of 31 of the 33 DAT patients, and of 24 controls.

5. I coded all of the data collected in neuropsychological and SPECT parts of the study onto specifically designed proformas and spreadsheets.

6. I carried out all of the statistical analyses described in the thesis using statistical packages.

Acknowledgements

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I particularly wish to thank John Hodges for nurturing and developing my interest in higher cortical function. He guided the development of the study, and was a constant source of encouragement and constructive criticism. I am deeply indebted to him for his support.

The proximity of the MRC Applied Psychology Unit to Addenbrooke's was very helpful in cultivating my interest in neuropsychology. In particular, Karalyn Patterson and Alan Baddeley were most helpful in introducing me to the complexities of cognitive neuropsychology. I would also like to thank Kenneth Miles of the Department of Nuclear Medicine. Statistical advice was provided by Ian Nimmo-Smith and Peter Watson of the MRC Applied Psychology Unit.

Finally, I would like to thank Roche Pharmaceuticals and Sandoz who provided the financial support for me to conduct my research. Above all, I thank my parents and my fiancee Margaret.

Chapter One

Introduction

Historical introduction

In 1907, Alois Alzheimer described the case of a 55-year-old woman who presented with memory impairment [4, 5]. She also exhibited decreased perceptivity, aphasia, lack of orientation, unpredictable behaviour, paranoid ideas, auditory hallucinations, and marked psychosocial incompetence. Post mortem revealed the presence of abnormal neurones with neurofibrillary tangles, and plaques (clusters of degenerative dendrites). This case report resulted in a flood of similar descriptions culminating in the use of the term Alzheimer's disease. Controversy raged over whether presenile and senile dementia were the same or different diseases, and the label Alzheimer's disease came to be applied to those cases of dementia occurring in patients under 65.

Over the past two decades it has become clear that Alzheimer pathology is responsible for many cases of dementia both below and above the age of 65, and the term Alzheimer's disease may now be applied, regardless of age of onset.

Despite advances in neuropsychological and neuroimaging techniques, it should be noted that a diagnosis of definite Alzheimer's disease (AD) can only be made when cognitive impairment during life is accompanied by proof of Alzheimer pathology from biopsy or post mortem. In the absence of such pathological proof, clinical criteria may be applied to make tentative diagnoses of probable or possible Alzheimer's disease, perhaps the most widely used being the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders, and Stroke - Alzheimer's Disease and Related Disorders Association) [219], which will be discussed further below. This thesis concerns patients with probable Alzheimer's, and hence the term dementia of Alzheimer type (DAT) will be applied. The subjects are, however, being enrolled into a neuropathological study, and I hope eventually to determine whether they have AD at post mortem.

Epidemiology

Dementia is defined as "a syndrome consisting of progressive impairment in two or more areas of cognition (i.e. memory, language, visuo-spatial and perceptual ability, thinking and problem solving, personality) sufficient to interfere with work, social function or relationships, in the absence of delirium or major non-organic psychiatric disorders (e.g. depression, schizophrenia)" [6].

The dementias are becoming increasingly important to society, in terms of both the social and economic costs. With the increasing longevity of the population, dementia is likely to become an ever increasing problem for health care. Dementia is largely a disorder of later life, affecting 5 to 8% of over 65s [326]. Above the age of 65, the prevalence of dementia doubles every five years, and reaches over 20% in 80

year olds. There are over one million sufferers in Britain, a third of whom are severely incapacitated. It is now the fourth commonest cause of death in Britain.

Alzheimer's disease is the commonest cause of dementia, accounting for approximately two-thirds of cases of dementia [326]. The aetiology is currently unknown [275], although there are associations with age, Down's syndrome, head injury and family history; indeed, in a small percentage of early-onset cases there is an autosomal dominant pattern of inheritance with the demonstration in such families of definite chromosome abnormalities. Familial cases with definite gene abnormalities have been described, affecting chromosomes 14 [290], 19 [258] and 21 [314].

Since this study is concerned primarily with aspects of neuropsychology of memory in DAT, a brief discussion regarding the components of memory and their neural substrates will be given first.

Subdivisions of memory

It has become clear that memory is not a unitary cognitive module, but itself comprises several components (see Figure 1.1).

One broad division is into explicit memory, (i.e. memories which can be brought to conscious level) and implicit memory, (i.e. memories which function at an unconscious level, e.g. priming effects and skills such as driving) [120]. Within explicit memory, there are further subdivisions into short-term or working memory (which refers to memories lasting for only a few seconds at most), and long-term memory.

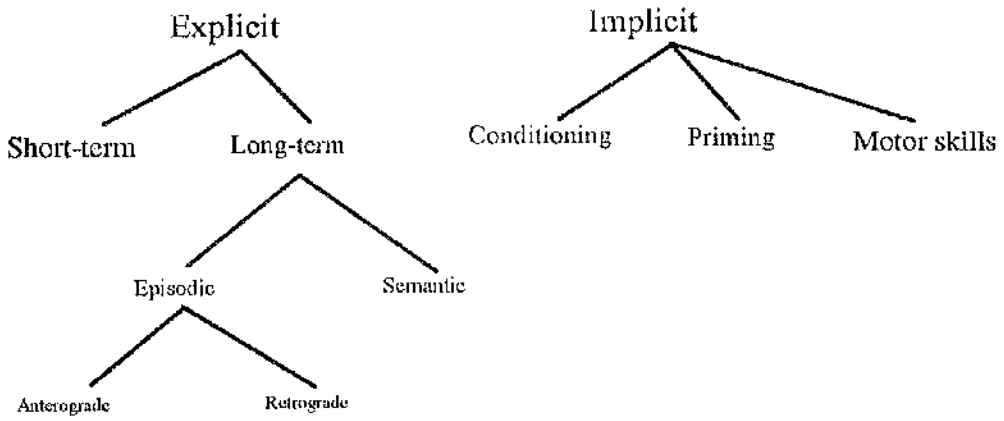
Working memory, although an apparently simple process, is in fact rather complex comprising a central executive component and two subsidiary slave systems [13]. The central executive is required for divided attention tasks, and involves the frontal lobes. The phonological loop, involving perisylvian language areas, is involved with the brief retention of verbal material (e.g. digit span). The other slave system is the visuo-spatial sketchpad which is responsible for the brief retention of visual information.

Long-term memory has been fractionated into episodic memory and semantic memory [328]. Episodic memory refers to contextual and time-tagged events (e.g. learning a list of ten words, or remembering details of a recent holiday). Episodic memory for events occurring after the onset of pathology is labelled anterograde memory, while memory for events before the onset of pathology is labelled retrograde or remote memory.

The term semantic memory is applied to the component of long-term memory containing knowledge of objects, facts and concepts as well as words and their meaning [182, 328, 329]. In contrast to episodic memory, semantic memory is culturally shared (rather than personal) and is not temporally specific. Tasks

dependent on semantic memory include object naming, generation of definitions for spoken words, word-picture and picture-picture matching and the generation of exemplars on category fluency tests (e.g. animals, vegetables etc.)

Figure 1.1 Subdivisions of memory
After Squire and Zola-Morgan [313]



The anatomy of memory

Attempts to localise these subcomponents of memory have met with some success [257]. Episodic memory appears to involve three components of the limbic system: the medial temporal lobe, the diencephalon and the basal forebrain. The hippocampus (including the dentate gyrus and subicular complex) and adjacent cortical areas (especially the entorhinal, perirhinal and parahippocampal cortices) are critical for the acquisition of new episodic memories [308]. The diencephalon (mammillary bodies, thalamus, mammillothalamic tract, medio-dorsal thalamic nucleus) and the basal forebrain (including the nucleus basalis of Meynert) are also important in the establishment and retrieval of episodic memories.

These structures (particularly the medial temporal complex) are functionally related to a series of cortical association areas interlocked by feedforward and feedback projections. It has been proposed that feedforward projections are directed at convergence zones from which reciprocating feedback projections originate [80]. The convergence zones in the association cortices would provide the substrate for retroactivation of the neural activities that took place during previous perception and thought processing, so as to form the apparent seamless content of recall [81].

Global amnesia may occur due to bilateral damage to one or more of the medial temporal lobes [293], the diencephalon [205] or the basal forebrain [83, 161]. Damage to any one of these structures causes amnesia, even if the other structures remain

intact [309]. The core anterograde amnesic deficit does not seem to vary with the anatomical site of the pathology. In a PET study of global amnesia, bilateral hypometabolism was seen in the frontal basal cortex, hippocampal region, thalamus and cingulate gyrus, regardless of the site of the lesion within these structures [107], suggesting that damage to any part of the functional unit leads to impaired function of the whole unit.

The finding that remote memory may be intact in amnesia [311] argues, however, that memory relies on the above system for only a limited period of time after learning. The above medial temporal - diencephalon - basal forebrain system is required at the time of learning and during a period thereafter, while a slow-developing, more permanent memory trace is established elsewhere, presumably in neocortex [308]. The period over which this process of consolidation occurs remains controversial but may extend over several years. The anatomical basis of very long-term personally based and more general semantic memory is less well established but more widely distributed cortical regions are almost certainly involved. Recent studies of patients with progressive, yet selective, loss of semantic memory have pointed to the dominant temporal neocortex as the critical area [144, 256]. By contrast, person-based semantic memory may depend upon the non-dominant temporal lobe [101, 103, 128].

Short-term memory is normal in amnesia resulting from hippocampal pathology [63]. As mentioned above, the central executive component appears to be anatomically subserved by the frontal lobes. The phonological loop is subserved by perisylvian language areas, while the visuospatial sketchpad utilises equivalent non-dominant areas.

Whereas explicit memory depends on an interaction between neocortex and the medial temporal - diencephalon - basal forebrain system, implicit memory depends on the neocortex and neostriatum [253, 343]. Thus, explicit and implicit memory appear to be subserved by different anatomical structures [307].

Pathology of AD

Brain weight in AD is reduced with respect to ageing controls. Although small numbers of both neuritic plaques and neurofibrillary tangles can be seen in the brains of older persons without dementia, the numbers and distribution of such plaques and tangles are the most useful discriminators of patients with AD.

AD can only be diagnosed with certainty by neuropathological confirmation of neocortical atrophy and neuronal loss [325], with intraneuronal tangles of paired helical filaments and extraneuronal plaques containing an amyloid core [323]. The presence of plaques and tangles correlates significantly with the presence of dementia

[356]. More recently, however, it has been claimed that synaptic loss may be the primary determinant of DAT, and that plaques and tangles may be only secondary [324]. These neuropathological changes are most marked in the medial temporal lobes, especially the transentorhinal region, the parahippocampal gyrus and the hippocampus [42, 337]. The higher-order posterior association areas in the parietal, temporal and occipital lobes are also heavily involved in the disease. Although primarily a cortical disease, there is also subcortical pathology, with neuronal loss in the nucleus basalis of Meynert and the nucleus locus coeruleus, with reduced acetyl choline and noradrenaline [39, 207, 355].

The typical pattern of spread is of initial transentorhinal pathology, followed by perihippocampal and subsequent isocortical involvement [42], but it is clear from isolated case reports of patients with highly atypical presentations (e.g. aphasia [123, 179, 259], visuo-spatial and perceptual dysfunction [121, 199], apraxia [124], hemiparesis and alien limb [74]) that AD can begin in other brain regions.

From our knowledge of the localisation of subcomponents of memory (discussed above) and of the pattern of spread of AD pathology, we might predict the order in which components of memory become impaired. Initial perihippocampal pathology would be expected to disrupt episodic memory. Subsequent spread to temporo-parietal association cortex should lead to semantic memory breakdown. Latterly, involvement of the frontal lobes by AD pathology should lead to executive dysfunction.

Clinical presentation of Alzheimer's disease

Clinically, DAT does not result in "global" cognitive impairment from the start of the illness, but progresses in a relatively predictable pattern through various stages. There is, however, considerable heterogeneity in the pattern of progression [38, 295]. The following is intended as a general overview of the topic and only a guide to the most common order of deterioration. The nature of the memory deficit will be addressed more fully in the next section.

Memory is almost invariably the first aspect of cognition to be impaired. Typically patients exhibit great difficulty in learning and retaining new information. Impaired delayed recall appears to be a particularly good indicator of early DAT [352, 353]. In clinical practice, this can be shown on tasks such as recall of a name and address after a delay of 5 to 10 minutes. Patients are often reasonably well orientated at this stage. This isolated memory impairment may continue for a number of years until other aspects of cognition become impaired [118, 201]

Although it is established that anterograde episodic memory is impaired even in minimal DAT, the nature of the episodic deficit is less clear. The relative

contributions of deficits in encoding, storage and retrieval to the memory impairment remain undecided. It is accepted that poor encoding contributes significantly [98], and that retrieval deficits do not appear to play a major role. The issue of whether DAT patients have normal or faster rate of forgetting is, however, controversial [26, 130, 187, 239].

It is evident that remote memory, both autobiographical and for public figures and events [148, 188, 280], is impaired in established disease. It is less clear, however, at what stage in the illness remote memory first becomes impaired. There is also debate regarding whether the remote memory impairment is due to loss of semantic knowledge or a retrieval deficit. The relation between remote memory and both anterograde memory and semantic memory has also been poorly characterised.

The onset of semantic memory impairment in DAT is variable: in some, it is present at clinical presentation. The earliest symptom of semantic memory impairment is often word-finding difficulty. Diminished vocabulary, poor naming with semantic paraphasias, and loss of general knowledge indicate the development of more severe semantic memory breakdown [149]. Category fluency appears to be a sensitive test for detecting early semantic memory disruption.

Working memory has been shown to be impaired in established DAT [14]. Indeed, DAT has been characterised as a combined "amnesic-dysexecutive" syndrome [10, 14, 236, 237]. It is less clear, however, at what stage in the illness this working memory impairment develops. Working memory has been shown to be relatively preserved in the very early stages of DAT [154, 281, 305] so that patients perform well on tests of verbal short-term memory such as digit span and those which stress the central executive component of working memory, particularly dual-performance tasks.

With progression, memory continues to deteriorate, resulting in a marked temporal disorientation, and the lexico-semantic impairment becomes more obvious, resulting in anomia and decreased comprehension [131]. Although phonology and syntax may show some minor deficits late in the disease, the aphasia is almost always fluent, even in advanced disease [8, 75, 104, 240, 261].

As the condition deteriorates, marked visuospatial and perceptual deficits occur [183, 220], often accompanied by hallucinations and paranoid delusions. Depression is also common [76]. Eventually, all aspects of cognition become impaired, and the patient exhibits features of amnesia, aphasia, agnosia, apraxia [92] etc. Personality disintegrates, and social misconduct and aggressive behaviour may occur. Primitive reflexes emerge [31, 111], and pyramidal and extrapyramidal signs occur [111, 225]. There is also a greater incidence of seizures and myoclonus [105]. Increasing dependency usually results in death some 5-10 years after diagnosis.

The diagnosis of DAT

It is clearly important to make the diagnosis of DAT with certainty early in the course of the disease, in order to counsel patients and their relatives about the likely prognosis, and also given the advent of drug therapies now available for DAT [85, 184]. As stated earlier, AD may only be diagnosed with certainty when dementia present during life is accompanied by neuropathological confirmation of tangles and plaques. As there is no definitive *in vivo* test (other than brain biopsy which is considered ethically unacceptable), clinical guidelines for diagnosis have been constructed. These criteria use clinical history, physical examination, and laboratory tests which aim to exclude other conditions. One of the most popular such criteria is that of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [219]. These require clinical evidence of presence of dementia, progressive memory impairment, onset between 40 and 90 years, and the absence of other brain disorders which could account for the symptoms, and have been shown to have high diagnostic accuracy [231], being at least 80% accurate in the diagnosis of pathologically verified AD [226, 339].

Neuropsychology of memory in DAT

The bulk of this thesis concerns the nature of the memory deficit seen in patients with early DAT. A detailed literature review of the various subcomponents of explicit memory affected by DAT will be included in the relevant chapter. The following section is a brief overview only which highlights the principal areas of controversy and sets the agenda for the remainder of the thesis.

Working memory

According to Baddeley's three-component model (outlined above), working memory comprises a phonological loop for manipulating and storing speech-based information and a visuospatial sketchpad that performs a similar function for visual and spatial information. Both are supervised by a central executive, which functions as an attentional control system [17, 18]. In the context of AD, most research has been directed at the central executive which plays a role in working memory, attention and problem solving.

The phonological loop in DAT

This component can be assessed by digit or letter span. Although normal in very early AD [211, 347], it becomes impaired in established disease [186, 187, 233, 305].

The visuospatial sketchpad in DAT

The nonverbal equivalent of the phonological loop is the visuospatial sketchpad. Although DAT patients are impaired in visuo-spatial short-term memory tasks such as the Corsi blocks [71], many visuospatial short-term memory tests draw on the central executive system [13], and it is not possible at present to determine whether the visuospatial sketchpad is impaired in DAT [234].

The central executive

The ability to perform two tasks simultaneously is often used as a measure of the central executive component of working memory. It is well established that patients with DAT perform poorly on dual performance based tasks [14, 15, 19, 282], although it is uncertain how early in the course of the disease such deficits are apparent [281]. This is of importance since many clinical neuropsychologists would not consider a diagnosis of possible DAT in patients with a pure progressive amnesic syndrome in the absence of executive or other deficits.

Another complicating factor relates to the concept of executive function. Many tests have claimed to be measures of executive function, varying from dual performance tasks to letter fluency to sorting tasks. These tests may stress differing aspects of executive function which might be differentially vulnerable to the effects of early DAT.

These issues will be further addressed in Chapter 5.

Episodic memory

Impairment of memory is the cardinal feature of DAT and is present to a marked degree in the vast majority of cases from early in the course of the disease. The nature of the anterograde memory deficit has now been extensively investigated using theoretically-based tests borrowed from cognitive psychology. Although the profound deficit in episodic memory has been attributed principally to defective encoding and storage of new information [122, 211, 347], there is also evidence of increased sensitivity to pro-active interference [56, 58]. The issue of whether the rate of forgetting is accelerated or normal is, however, controversial. Some claim that forgetting is accelerated [59, 186, 239, 352], while others claim that it is normal [26, 72, 187]. This issue has importance for understanding the nature of the episodic memory deficit in DAT.

It is known that left- and right-sided medial temporal structures are implicated in memory for verbal and nonverbal material, respectively [252]. In established DAT, with bilateral perihippocampal pathology, one might expect to see anterograde episodic memory impairment for both verbal and nonverbal material. In the early stages of DAT, however, AD pathology may be asymmetrical or even unilateral [113,

132]. It might be predicted therefore that some such minimally affected DAT patients would show a material-specific memory deficit. Studies addressing this issue have given conflicting results [29, 94, 119], largely as a result of methodological differences. Again, this is important for our understanding of the cognitive deficits early in the course of DAT. Chapter 6 studies the nature of the anterograde episodic memory deficit in DAT, with particular attention to the issues of rate of forgetting and material-specificity.

Remote memory

Several studies of patients with established DAT have shown remote memory impairment, for both public and autobiographical facts. In the majority of studies, the memory deficit also shows a mild temporal gradient, early-life memories being relatively spared [25, 148, 188]. Theoretical explanations for the finding of a temporal gradient will be discussed in Chapter 3.

Although remote memory is known to be impaired in established DAT, it is not clear at what stage of the illness this occurs. Moreover, as stated above, not all studies have found a temporal gradient. This may be related to test design. Another important and unresearched area is the relationship of remote memory to anterograde memory. Individual case reports of patients with non-dementing disorders have highlighted dissociations between anterograde and remote memory, e.g. isolated anterograde amnesia [68, 303, 310, 312, 361, 367] and isolated retrograde amnesia [116, 173, 174, 208, 247]. Group studies of DAT have not addressed this issue, which has relevance to our understanding of the systems underlying the establishment of new memories and the storage/retrieval of old memories. Another issue that has not been explored is the relationship between person-specific knowledge (i.e. related to famous persons) and more general semantic knowledge. This is relevant since many tests of remote memory have employed famous faces tests and this domain of knowledge may be represented independently [103]. Finally, although the nature of the cognitive deficit underlying the remote memory impairment seen in DAT has been studied using modern information processing models of face processing [148], no study has explored accessing person-specific information via different inputs, e.g. presenting faces and names of famous people. Investigation of these different domains may inform our understanding of famous face and name processing in general as well as increasing our database regarding the neuropsychological deficits found in DAT.

Research in the area of remote memory is plagued by methodological problems: if a patient fails to identify a famous face, can we be sure that this represents the development of remote memory impairment, or did the patient never previously know the identity of the famous person ? Longitudinal studies are more

methodologically sound for this type of analysis, as the patients can act as their own controls, but have been performed only very rarely. A further major controversy in DAT is whether impaired semantic knowledge is due to loss of storage of the memory, or to failure to access the memory [149]. One way of addressing this issue (which is yet to be employed) is an item-by-item approach over time: if it could be shown that subjects lost the ability to identify previously known faces, then this would be in keeping with loss of storage. Alternatively, if the overall picture was more variable, with some faces being recognised only on year one, and others on year two but not year one, then this would be more in keeping with a retrieval deficit, i.e. an access deficit.

Memory for famous faces and names in DAT are the focus of Chapters 3 and 9.

Autobiographical memory

It is clear that autobiographical memory, which is one of the most vital of human faculties, involves complex mnemonic retrieval processes. Models of remote memory processing have been developed which conceive recollection and remembering as being a dynamic cognitive operation involving problem solving, cross-checking, verification and inference [245]. Although executive function has been implicated in these complex retrieval processes [90, 91, 141], the extent of the role of frontal executive function in autobiographical memory retrieval remains controversial.

Turning to DAT, previous studies have shown impaired autobiographical memory in DAT [78, 188, 280], but again the stage at which this occurs and the consistency across cases is not clear. Since executive function is often also impaired in DAT, there is an opportunity to investigate the important issue of the relationship between autobiographical memory and executive function. To date, results of such correlations are controversial. By studying the relationship between executive function as a whole, and autobiographical memory as a whole, some studies have overlooked interrelationships between subcomponents of both executive function and autobiographical memory. For instance, it has been proposed that autobiographical memory is not a unitary entity but comprises two separable components - personal semantic and personal incident [190]. These questions are addressed in greater detail in Chapter 5.

Another issue is whether the fractionation of remote memory into memory for public and autobiographical facts is justified, or is an artificial distinction. Individual case reports have claimed to show selective deficits of public [87, 101, 174] or autobiographical memory [79, 319]. A more powerful way of demonstrating a true fractionation would be to study remote memory for public and autobiographical

memory longitudinally, and to see if there was any dissociation in the deterioration between the two components. This is done in Chapter 9.

Semantic memory

Semantic memory appears to be impaired in DAT [58, 126, 155, 213, 248, 347]. Evidence for this includes findings on category fluency [58, 143, 146, 147, 149, 213, 228, 229, 249, 276, 278, 350], naming [21, 41, 147, 155, 213, 301], word-picture matching and tests using semantic batteries. Further evidence of semantic memory impairment in DAT arises from studies of intrusion errors on word list recall [114, 163], and the inability to benefit from semantic organisation [348].

Although some investigators feel that semantic impairment in DAT is due to lack of access [22, 23, 242], the majority of workers feel that it is due to a storage deficit [65-67, 137, 149, 155, 213]. Chan *et al* [65], using a multi-dimensional scaling technique, have shown that the impairment in category fluency performance reflects a fundamental change in the structure of the semantic representations.

It appears that the onset of semantic memory impairment in DAT is variable [143]. Semantic memory is mildly, though significantly, impaired at the very earliest stages of DAT, but becomes a major feature of DAT in later stages of the disease. The semantic impairment in early disease is largely due to a consistent impairment across the range of tests in a subgroup of individuals. The nature of the semantic memory deficit in DAT is not a central concern of this thesis, except the issue of the relationship between general and person-specific semantics (see Chapter 3).

A related topic is the question of naming without semantics. With regard to current models of naming, it is widely held that naming only occurs if the subject can identify the object, i.e. the route from perception to naming must involve semantics [62, 156]. Although this view is widely held, it has been claimed recently that naming may be possible in the absence of semantics, i.e. there may be a direct route from perception to naming, bypassing semantics and that this "non-semantic naming route" may remain functional in the face of semantic deterioration in DAT giving rise to the phenomenon of naming without semantics [192, 193, 298]. As a result of the studies of face identification and naming in DAT, I have been able to address this theoretical point in Chapter 4.

Imaging in DAT

Other than neuropsychology, another major means of investigating DAT *in vivo* is by imaging. Imaging can study brain structure (by computed tomography or magnetic

resonance imaging) or function (by positron emission tomography or single photon emission computed tomography).

The imaging modality most widely available for clinical investigation of dementia is CT scanning. Although CT may show generalised cortical atrophy in the latter stages of degenerative dementia, scanning is done primarily to exclude other pathologies such as hydrocephalus or tumours. In one study, CT scanning elicited treatable pathology in 10% of patients presenting with dementia [43]. More detailed CT analysis, particularly employing temporal lobe orientated cuts, now appears to be able to detect initial perihippocampal pathology early in the course of DAT [168, 169].

The superior resolution of MRI [287] allows volumetric studies of the hippocampus in early DAT, and is useful diagnostically [102, 162, 181, 291]. In particular, the combination of hippocampal atrophy and absence of white matter changes on MRI is strongly suggestive of AD [292].

Functional imaging in the form of PET (positron emission tomography) remains largely a research tool [194, 215, 351]. Perfusion and metabolism in individual cortical areas may be assessed, a reduction being suggestive of cortical pathology.

SPECT (single photon emission computed tomography) is more widely available, and is addressed in this thesis. Classically, Alzheimer's disease tends to show a pattern of temporoparietal hypoperfusion [164, 171, 202, 218, 230, 320], followed by frontal hypoperfusion in more advanced disease (in contrast with the frontal or temporal changes seen in focal lobar atrophy [241] or the patchy tracer uptake seen in vascular dementia [93]). However, more recently, it has been claimed that the pattern of regional cerebral blood flow in DAT is much more heterogeneous [338, 340, 341].

Another issue relates to whether SPECT abnormalities become more noticeable with worsening disease progression. Some studies have found SPECT to be of limited use in staging DAT [164, 320]. It is, however, unclear at what stage in the illness SPECT becomes abnormal: it appears that SPECT regional cerebral blood flow may be normal in minimal DAT when memory is impaired and a clinical diagnosis of DAT is possible [266, 338].

Although the main thrust of this thesis concerns a longitudinal study of the neuropsychology of memory in DAT, I also analysed cross-sectional data regarding SPECT in DAT, primarily to ascertain the relative use of neuropsychology and SPECT imaging in the diagnosis and staging of DAT. This is addressed in Chapter 7.

Aims

It should be apparent from this brief review of the literature that although there has been considerable neuropsychological research on the memory impairment in DAT, many important questions remain unanswered. Similarly, the role of SPECT imaging in the diagnosis of DAT is not clear. The aims of this thesis (listed below) are to explore several theoretically-motivated and practical aspects of memory in DAT, as well as the use of SPECT scanning in the diagnosis and staging of DAT.

Memory for faces and names in DAT

How early in the course of DAT does this component of remote memory impairment occur ?

Is there a temporal gradient, and if so, how steep is it ?

What is the relationship between remote and anterograde episodic memory ?

What is the relationship between person-specific remote memory and general semantic memory ?

At what stage in the cognitive model of face processing does the remote memory impairment lie ?

What is the relationship between person-specific remote memory accessed by faces and that accessed by names ?

Naming without semantics

With reference to a test of famous face identification and naming, is there any evidence of naming without semantics, i.e. can any of patients ever name a famous face and yet have no other identifying knowledge about the person ?

The role of frontal executive function in autobiographical memory in DAT

Is executive function impaired in DAT, and if so, at what stage ?

At what stage is autobiographical memory impaired in DAT ? Is there a temporal gradient ?

Do the data support the contention that executive function is implicated in the retrieval of autobiographical memory ?

Is there evidence for the further fractionation of executive function and autobiographical memory ?

The nature of the anterograde memory deficit in DAT

What are the relative contributions of encoding, storage and retrieval to the anterograde memory in DAT ?

Is the learning rate impaired in DAT ?

Is the forgetting rate accelerated in DAT ?

Is there evidence of material-specificity for memory in early DAT ?

How useful are episodic memory measures in staging DAT ?

The use of neuropsychology of memory and SPECT imaging in the diagnosis and staging of dementia of DAT

How relatively useful are neuropsychological tests of memory and SPECT imaging in diagnosing and staging DAT ?

What does SPECT tell us about the pattern of spread of DAT ?

Longitudinal decline of memory in DAT

Which aspects of memory decline longitudinally in DAT patients with minimal and mild disease ?

How do the longitudinal data contribute to diagnosing and staging DAT ?

Longitudinal study of remote memory in DAT

Is there support for the fractionation of remote memory for public and autobiographical facts ?

If there is a deterioration in memory for public figures, which cognitive component of face processing is responsible ?

If there is a decline in identification of famous people longitudinally, is this due to loss of storage, or a failure to access this information ?

Design

This study is a longitudinal prospective study of the neuropsychology of memory in patients with early DAT and in controls. SPECT scanning was done at the time of initial neuropsychological testing. Although, as detailed in my initial MD proposal, I had intended to repeat the SPECT scanning after one year, this was not done. This was partly because other investigators have found little or no change in SPECT scanning over one year, particularly in minimal cases. Another problem is that, by the time I wanted to repeat the scans, the SPECT scanner was only available for research on weekday evenings. As Cambridge has only a small population, my subjects are scattered throughout East Anglia, some living up to 100 miles away, and logistically it

would have proved impossible to have my out-patients scanned late on weekday evenings, and then require their carers to drive home long distances. Analysis of cross-sectional data at year 1 showed that SPECT scanning was of limited use in staging DAT severity. I felt, therefore, that SPECT scanning after one year would be most unlikely to detect progression of DAT.

Chapter Two

Methods

Subject groups

Two groups consisting of a total of 63 subjects participated in the neuropsychological study: 33 patients with DAT (21 females and 12 males) and 30 neurologically intact normal control subjects (16 females and 14 males). Written informed consent was obtained from all subjects or the caregivers, where appropriate.

The DAT subjects were chosen from approximately 50 patients undergoing prospective evaluation at the University of Cambridge Neurology unit who were willing to be enrolled into a longitudinal study of remote memory and related cognitive deficits in DAT. Subjects' consent was obtained according to the declaration of Helsinki. The diagnosis of probable DAT was made by a neurologist and a psychiatrist according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), which consist of inclusion and exclusion criteria [219]. All patients presented with a history of a one to four year progressive cognitive impairment predominantly affecting memory and were shown on formal neuropsychological assessment to have deficits in two or more cognitive domains. This testing was independent of the project detailed in this thesis. All achieved a score of 4 or less on the Hachinski Scale [127], thus reducing the likelihood of multi-infarct dementia. Patients with a past history of known or suspected transient cerebral ischaemic event or stroke, alcoholism, head injury or major medical illnesses (e.g. cancer, anaemia, thyroid dysfunction etc.) were excluded, as were those with major depression. All patients were examined by a neurologist and underwent CT or MRI scanning, together with the usual battery of screening blood tests, to exclude treatable causes of dementia. All of the probable DAT patients were living with caregivers without institutional support.

Normal control subjects for neuropsychological testing were either spouses of patients, or in-patients with non-cerebral pathology (e.g. cervical spondylosis, peripheral neuropathy). Subjects with a history of alcoholism, drug abuse, learning disability or psychiatric illness were excluded. They were matched with the DAT patients on the basis of age and education level.

SPECT scans were obtained on 31 of the 33 DAT patients. For SPECT control data, it was felt unethical to subject the neuropsychological controls to SPECT scanning. I therefore used 24 age-matched controls who attended the Memory Clinic but who were found to perform normally on a range of standard clinical neuropsychological tasks. All were found to perform normally on detailed neuropsychological testing which included subtests of the Wechsler Adult Intelligence Scale-Revised and Visual Object and Space Perception battery, the Recognition Memory Test and the Graded Naming Test. These patients were followed up

longitudinally and were found to have no subsequent clinical or neuropsychological deterioration. They were also seen by a Consultant Psychiatrist and found to have no major psychiatric illness: they fall, therefore, into the category of "worried well". I therefore felt justified in using the SPECT scans of these patients as controls. There was no significant difference in age between the DAT patients and SPECT controls (t[d.f. 53]=0.9, $p>0.05$).

For some analyses, the DAT patients were divided into two sub-groups on the basis of their scores on the Mini Mental State Examination [109]. As none of the subjects, even the most impaired, could be considered severely demented (for example, no patient was institutionalised or greater than grade 2 (moderate) on the Clinical Dementia Rating Scale [34], the two sub-groups have been designated minimal and mild. The MMSE score ranges for the two sub-groups were 24-30 for minimal and 17-23 for mild. The upper cut-off of 24 was chosen since this is conventionally regarded as the lower limit of normality.

The numbers of subjects in each of the sub-groups, and their mean ages, years of education and MMSE scores, are shown in Table 2.1, along with values for the same dimensions for the control group. One-way ANOVA revealed no significant difference for age (F (2,60)=4.7, $p>0.05$) or for education (F (2,60)=2.3, $p>0.05$). With regard to pre-morbid IQ as assessed by the NART [244], mild DAT patients performed significantly worse than controls and minimal DAT patients (F (2,60)=8.9, $p<.01$). However, this may represent the mild surface dyslexia which has recently been documented in mild DAT patients [255], rather than suggesting that mild DAT patients had lower pre-morbid IQs.

It should be noted that the MMSE is very unreliable for discriminating DAT patients from controls, and was not used in my study for diagnostic purposes. Indeed, some of my DAT patients achieved a MMSE of 30, while controls scored as low as 26. All patients have been followed up, and none have been found to improve. Consequently, none have been excluded from the analysis.

24 of the original 33 DAT patients were retested after one year. Reasons for failure of follow-up were inability to comply with testing due to dementia severity, intervening development of cerebrovascular disease and reluctance to be re-tested. To ensure that any deterioration in the DAT patients over the year was due to DAT pathology and not simply ageing, 5 of the controls were retested after one year to see if ageing over one year might lead to a deterioration in neuropsychological test performance.

Table 2.1. Mean (S.D.) age, education and MMSE scores for the DAT cases and normal control subjects

	Neuropsychology controls	DAT			SPECT controls
		overall	minimal	mild	
	n=30	*n*=33	*n*=17	*n*=16	*n=24*
Age	67.9 (8.7)	69.9 (8.6)	73.1 (8.2)	66.2 (8.0)	65.4 (8.2)
Education (yrs)	11.0 (2.9)	11.5 (3.2)	12.5 (3.4)	10.3 (2.6)	
IQ (NART)	114 (7.8)	113 (9.3)	118 (6.9)	108 (8.7)	
MMSE score	29.5 (0.7)	23.5 (4.1)	26.2 (2.2)	20.3 (3.3)	
Range	26-30	(17-30)	24-30	17-23	

Neuropsychological Tests

Table 2.2 illustrates the memory tests administered to the subjects.

Table 2.2 Memory tests administered to DAT patients and controls

Component of memory	Test
Working	Della Sala *et al*'s dual performance task
	Dual performance task from TEA
	Letter fluency
Anterograde episodic	Logical memory
	CERAD word list
	Doors and People Test
Autobiographical	Autobiographical Memory Interview
	Autobiographical fluency
Remote memory	Famous Face recognition, identification, naming
	Famous Name recognition, identification
Semantic memory	Category fluency
	Picture naming
	Word-picture matching
	Naming to description
	Pyramids & Palm Trees Test

Tests of executive function

1. Della Sala *et al*'s dual performance task

This task, modified from Baddeley *et al*'s visual tracking-digit span test [13, 14], has been developed by Della Sala *et al* [89]. The current version has been devised as a dual performance task which can be used in the clinic with minimal equipment.

The subject's digit span is first determined in the usual way by administering progressively lengthening strings of digits, which are read to the subject at a rate of one per second. Then sequences of digits at the subject's span (e.g. five or six) are next continuously given for two minutes (i.e. 120 seconds), and the number of sequences correct is determined. In the second part of the test, the subjects are presented with a trail of boxes, and are required to put a cross in each box, following the trail. The number of boxes filled in two minutes is determined.

The dual performance test is next performed. The subject is required to cross boxes in the trail while simultaneously being presented with sequences of digits at their span which they have to repeat. A dual performance decrement was calculated, by using the boxes and digit span information, according to the following formula:

Dual task decrement = (120 seconds/no boxes dual task)/(proportion of digit span sequences correct on dual task)-(120 seconds/no boxes single task)/(proportion of digit span sequences correct on single task)

The dual task decrement is, therefore, an expression of how many seconds extra it takes the subject to fill one box on the dual task as opposed to the single task, with an adjustment made for performance on digit span sequences completed correctly. In performing this task, subjects may employ different strategies. They may concentrate on the digit span sequences in the dual task performance, and consequently fill fewer boxes. Alternatively, they may concentrate on box filling, at the expense of the digit span sequences. In order to adjust for these separate strategies, the dual task performance utilises both sets of data in order to give a measure of dual task, or central executive function.

In order to correlate performance on dual task measures with other tests of memory, I took the negative of the dual task decrement and used this as a measure of dual task performance.

2. Dual performance task from the Test of Everyday Attention (TEA)

In this test [274], the subject is first presented with an array based on the telephone directory "yellow pages", and is required to look down four columns and to mark when two symbols side by side are identical There are twenty pairs to be detected.

The number of symbols correctly marked and the time taken are measured. The dual performance component involves repeating the above measure, but with a separate auditory component; whilst repeating the symbol marking test, the subject is required to listen to a sequence of tones, and has to count the number of tones in each sequence and say how many were in each sequence. A dual performance decrement is calculated using the number of symbols counted, the time taken and the proportion of tones counted, in the following manner.

Dual task decrement =(time taken dual task/symbols counted dual task)/(proportion of tone sequences correct)-(time taken single task/symbols counted single task)

The dual task decrement is an expression of the extra time taken to mark one symbol on the yellow pages test with respect to the single test, with an allowance made for performance on tone counting. The negative of the dual task decrement is taken as a measure of dual task performance.

3. FAS letter fluency

In this test [33], the subject is asked to give as many words as possible beginning with a given letter in one minute. The letters F, A and S are used. The subject is asked to avoid people's names or place names, and to avoid words derived from the same stem, (e.g. follow, followed, following).

Tests of anterograde memory

1. Logical memory

The logical memory component of the Wechsler Memory Scale-Revised (WMS-R) was used as it is a widely used measure of anterograde memory, and it has been shown that impaired delayed recall is a sensitive discriminator of DAT patients from controls [317]. Two paragraphs are read out to the subject. After each administration, the subject is asked to give as complete an account of the story as possible. After 30 minutes, the subject is asked to recall as much of each story as possible.

2. CERAD word list

The word list from the CERAD (Consortium to Establish a Register in Alzheimer's Disease) test battery was used as this has been used extensively in the centres comprising CERAD, and allowed me to compare my patients with the CERAD patients [232, 352, 353].

The subject is presented with ten printed words on single cards, and asked to read each word out loud. Immediate recall of the ten words is then tested. This procedure is then repeated twice using the same word list but with the words in a different order each time. After five minutes, the subject is asked to recall the words with no time limit. The subject is then presented with a set of 20 words on cards, half of which were on the original list. After the presentation of each word, the subject is asked if the word was on the original list. The mean of the number of words correctly recognised as either being on the original list or not is used as a measure of recognition. The test thus gives data on immediate verbal recall, delayed verbal recall and delayed verbal recognition.

3. Doors and People Test

This test which has recently been developed by Baddeley, Emslie and Nimmo-Smith [16] was used since it includes parallel recall- and recognition-based tests of verbal and nonverbal memory.

Nonverbal recognition (The Doors Test)

For nonverbal recognition, coloured photographs of doors are shown to the subject. The test is split into two parts (A and B). In each, 12 'target' doors are shown individually to the subject at three second intervals, followed by the same targets presented in a 2x2 array with three other distractor items all of which fit the same general label (e.g. church door). The subject has to pick out the one, out of the four, that has been shown before. Set B is harder than A and was not given unless the subject scored 9 or more on set A. (This was the original instructions for the test. The final published form recommends giving both sets A and B since this provides a more reliable measure of performance.) One mark is given for each correct response and scaled scores are derived for the combined Set A and B score. If the subject had not gone on to complete Set B, a scaled score for set A was derived and used as the final score.

Nonverbal recall (The Shapes Test)

Four simple drawings are shown to the patient, who is asked to copy them. The subject is then asked to draw them from memory. The drawings are then shown individually to the subject, each for five seconds. The subject is then required to draw each of them immediately from memory. This is repeated, such that three trials of immediate recall occur. Following a delay (see below for sequence of tests), the subject is required to draw the shapes again from memory. All four comprise a readily drawn version of a cross, varying in overall shape (square or elongated), and in the characteristic features of the crux and the end of the four arms. As with the 'doors', they have an obvious but unhelpful verbal label, namely a "cross". The drawings are

scored according to criteria described by Baddeley *et al* [16]. The maximum score for each drawing is 3, with the combined score over three trials used to obtain the scaled score. The difference between the initial and delayed drawing raw scores is used to obtain a scaled forgetting score.

Verbal recognition (The Names Test)

Names are used as the stimulus material, with each item comprising a forename and a surname (e.g. Diane Neeson). As with the nonverbal recognition test there are two subtests (A and B). In set A, 12 female names are shown to the subject at three second intervals. Then each name is shown in a 2x2 array, together with three distractors, and the subject is required to recognise the items presented before. The three distractor items always have the same forename as the distractor item. Set B uses male names and is harder than set A and was not given unless the subject scored 9 or more on set A. As with the nonverbal recognition test, one mark is given for each correct response and scaled scores obtained for the combined Set A and B score, unless the subject did not complete set B, in which case the scaled score for set A was used.

Verbal recall (The Person Test)

This requires the subject to learn the full names of four characters. Each name comprises a forename and surname (e.g. Cuthbert Cattermole) and is presented with a photograph, representing the person. The name and photograph are linked by telling the subject the occupation of the person (e.g. 'This if the minister. His name is Cuthbert Cattermole'). All four names are presented for three seconds followed by the recall stage in which the subject is cued to recall the name given the occupation (e.g. 'What was the minister's name?'). There are three trials to learn the names, unless the subject recalls all the names on a particular trial, at which point the test is terminated. Subsequently, delayed recall of the names is tested (see below for sequence of tests). One mark is given for each forename and surname correctly recalled, plus an extra mark for a correct pairing. Scores from the three trials are combined and used to derive a scaled score. If the test is terminated early, as indicated above, maximum marks are given for the remaining trials. A verbal recall forgetting score is obtained by subtracting the raw score on delayed recall from that on the final trial from the initial test. A scaled score is derived from this difference.

The order of presentation of tests is as follows: Verbal recall, nonverbal recognition, delayed verbal recall, nonverbal recall, verbal recognition, and delayed nonverbal recall. The raw scores were converted into scaled scores for each subtest by reference to published normative data based on a stratified sample of 245 control subjects [16].

Overall score

An overall score was computed by combining the scaled score from the four (non-delayed) subtests and obtaining a further scaled overall score.

Nonverbal versus verbal memory

The overall score can be broken down so as to contrast nonverbal and verbal scores. The scaled scores for the verbal recall and recognition tests are combined and a scaled total verbal memory score derived. The same procedure is used to combine nonverbal recall and recognition.

Nonverbal/verbal discrepancies

An alternative way of exploring the relative deficit in nonverbal or verbal memory is to obtain a nonverbal-verbal discrepancy score. These are computed by subtracting the two scaled verbal scores from the sum of the two nonverbal scaled scores. This measure was used to derive a further scaled score of nonverbal/verbal discrepancy, obtained from Baddeley *et al* [16].

Recall-recognition discrepancies

A total recall score was computed by combining the scaled scores for the two recall tests and obtaining a further scaled score. A total recognition score was obtained and scaled in the same manner. The difference between these scores was computed and converted into a scaled score.

Forgetting scores

The difference between the initial and delayed recall scores is used to obtain a scaled forgetting score. A verbal recall forgetting score is obtained by subtracting the raw score on delayed recall from that on the final trial from the initial test. A scaled score is derived from this difference. A total forgetting score was obtained by combining the scaled forgetting scores for the nonverbal and verbal forgetting measures described above and then deriving a further scaled score.

Tests of remote memory

1. Famous Faces Test

I used a modified and updated version of the famous faces test described by Hodges and Ward [150]. Fifty target photographs of prominent public figures were selected (see Appendix). Every effort was made to select faces of people who had remained famous for a limited period, preferably a single decade between the 1940s and 1980s. There were 10 photographs from each of the five decades. The photographs included politicians and statesmen, stage, film and TV personalities, and sportsmen. Black and white portrait photographs were used.

For each target photograph, three non-famous photographs were selected as foils. These were of the same age and sex, and from the same era as the target. The photographs of non-famous persons were selected from a wide variety of sources including year books, old magazines and newspapers.

Administration

I changed the administration of the test slightly between years 1 and 2. I shall firstly detail the administration on year 1.

Each target photograph was presented in a 2x2 array with its three matched foils. The position of the target was randomised with an overall balanced design. The test therefore consisted of 50 individually presented arrays. The order of the target photographs was arranged so that each block of five contained a photograph from each decade.

For each photograph there were three potential parts to the test: recognition, naming and identification.

1. Recognition. Subjects were presented with each array of four photographs and given the following instruction: "Only one of these four photographs is of a famous person. Can you point to the one you think is the famous person?" If incorrect, the target photograph was pointed out to the subject.

2. Naming. Subjects were then asked to name the famous person represented. Only a correct full name (i.e. first and last names) was accepted. If correct, subjects passed on to the next item in the test. If incorrect (error of omission or commission), the subject then proceeded to the third (identification) part for that item.

3. Identification. For un-named faces, subjects were encouraged to provide a detailed description of the famous person represented. No clues were provided but the examiner probed for further details to obtain the subject's most specific description using standard probes. For instance, in response to "a politician" the examiner asked what position did he/she hold and what party did they represent. For "actor or actress" subjects were asked what film or TV series they appeared in, etc. Responses scored as correct contained specific identifying information (e.g. Glenda Jackson "She's the actress who's now a Labour MP"; John Profumo "He's the Tory Minister who had the sex scandal"). Incorrect responses were generic or vague non-identifying statements (e.g. "a famous film star"; "the foreign politician" etc.)

Scores were thereby obtained for the overall total correct and for the items for each decade in each of the three test conditions as follows:

1. Recognition: the number correctly recognised as famous (chance level 25%, i.e. 12.5/50).

2. Naming: the number correctly named without cues.

3. Identification: the number of items correct on spontaneous (uncued) naming plus those producing specific identifying information.

It can be seen that I have assumed that correct naming automatically implies correct identifying information. However, proponents of naming without semantics would argue that this assumption is not valid. On the second year, I therefore tested in the following order: recognition, identification and naming. I could thereby assess whether preserved naming in the absence of semantic identifying information ever occurred

2. Famous Names Test

On a separate occasion from the administration of the famous faces test, I administered a famous names test. The same fifty famous people were used in this test. However, instead of being shown photographs, the subjects were shown cards with four names, one being famous with three foils.

Administration

Each target name was presented with three matched foils. The position of the target was randomised with an overall balanced design. The test therefore consisted of 50 individually presented arrays. The order of the target photographs was arranged so that each block of five contained a name from each decade.

For each name there were two potential parts to the test: recognition and identification.

1. Recognition. Subjects were presented with each array of four names and given the following instruction: "Only one of these four names is of a famous person. Can you point to the one you think is the famous person?" If incorrect, the target name was pointed out to the subject.

2. Identification.

Subjects were encouraged to provide a detailed description of the famous person represented. No clues were provided but the examiner probed for further details to obtain the subject's most specific description using standard probes, as in the famous faces test.

Scores were thereby obtained for the overall total correct and for the items for each decade in each of the two test conditions as follows:

1. Recognition: the number correctly recognised as famous (chance level 25%, i.e. 12.5/50)

2. Identification: the number whose identity was correctly established

Tests of autobiographical memory

1. Autobiographical Memory Interview

This test, developed by Kopelman *et al* [189], assesses personal semantic and autobiographical incident memory across three time periods: childhood, early adulthood, recent life. For each time period, the subject is asked to give personal semantic information (e.g. address of primary school) and autobiographical incident information (e.g. a particular incident occurring in childhood).

Some of the questions in the original test for the most recent time period referred to recent hospital attendances and are likely to be assessing anterograde memory rather than recent remote memory. I therefore modified the questions for the late adulthood time period to try to assess memory for events occurring before the onset of the pathology (e.g. an incident occurring on holiday prior to onset of memory problems).

Previous tests of autobiographical memory, including the AMI, had led to ceiling effects in controls [189]. This led to the development of a fluency-based test in an effort to avoid the ceiling effect, viz. autobiographical fluency.

2. Autobiographical fluency

In this fluency test [96], subjects are required to produce as many exemplars as possible in ninety seconds for each of the following six categories: names and incidents, each for childhood, early adulthood and late adulthood. For names, the subject has to produce as many names of people met in the particular time period. No detail is required regarding the names. For incidents, the subject is required to produce as many unique incidents as possible in the time given. As soon as the tester is satisfied that the subject is describing a unique incident, the subject is asked to move on to another example.

The problem of confounding recent remote memory with anterograde memory cannot be wholly avoided. However, recent remote memory was arbitrarily defined as referring to that part of the patient's life over the age of forty.

The above two tests draw on the same core of autobiographical knowledge. However, the AMI is more structured, and provides specific contextual cues.

Tests of semantic memory

A battery of tests, all employing one consistent set of stimulus items, has been designed to assess input to and output from central representational knowledge about the same group of items via different sensory modalities [144, 149]. It contains 48 items chosen to represent three categories of animals (land animals, sea creatures and

birds) and three categories of man-made items (household items, vehicles and musical instruments) matched for category prototypicality and word frequency. They were chose from the corpus of line drawings by Snodgrass and Vanderwart [302]. The full battery consists of seven subtests but only four will be considered here:

1. Category fluency for each of the 6 main categories plus two lower order categories (breeds of dog and types of boat)
2. Naming of all 48 line drawings without cueing
3. Naming in response to a verbal description (e.g. "What do you call the large African animal with a curved horn on its head?")
4. Word-picture matching to spoken word using within-category arrays (the original battery used arrays of 6 items all from the same category, such as land animals, but in the subsequent version arrays of 8 are now used which contain two foils not otherwise included in the test battery).

In addition, I employed a non-verbal test of semantic memory; the Pyramids and Palm Trees Test [153] three-picture version. This test requires subjects to match conceptually related pictures (the word version was not used in this study). For instance, the target picture of an Egyptian pyramid is presented above two drawings depicting a palm tree and a fir tree, and the subject is asked to judge which one goes with the pyramid. Other examples are spectacles with eye and ear, saddle with goat and horse. A total of 52 triads are presented.

SPECT imaging

31 of the 33 subjects who were given the neuropsychological battery were also scanned by means of functional imaging. As this study involves administration of radioactive substances to patients, a certificate issued by the Administration of Radioactive Substances Advisory Committee (ARSAC) of the Department of Health was obtained, issued to Dr K Miles, Consultant in Nuclear Medicine. SPECT (single photon emission computed tomography) was used to determine regional cerebral blood flow. It has been shown using PET (positron emission tomography) that in dementia, there is no uncoupling between cerebral blood flow and tissue metabolism [110].

A rCBF (regional cerebral blood flow) deficit in an ROI (region of interest) may be due to local pathology. Alternatively, the affected region may be structurally intact, but simply be functionally deafferented. For example, the temporo-parietal hypoperfusion seen in early DAT may be due to temporoparietal DAT pathology. Alternatively, the pathology may be restricted to the perihippocampal and basal

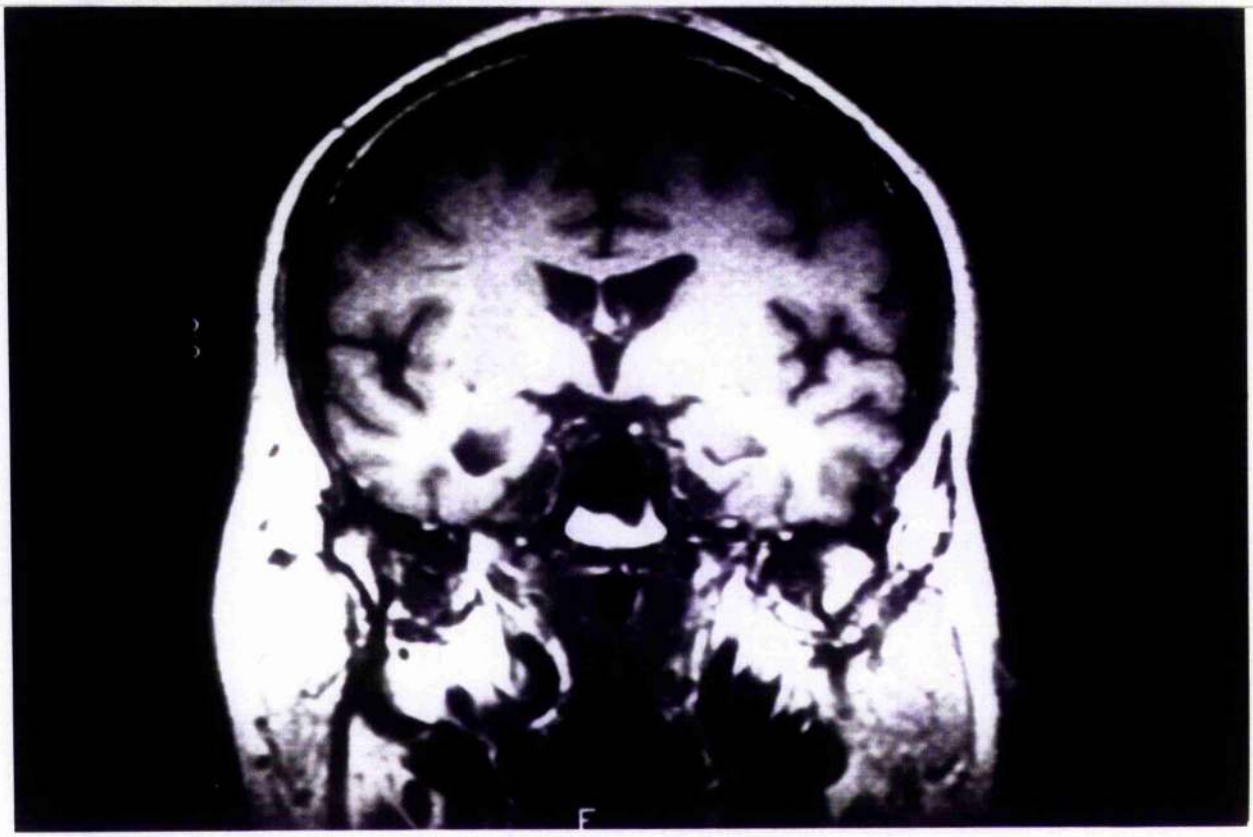
forebrain, with the reduction in temporoparietal rCBF simply reflecting functional deafferentation.

HMPAO (hexamethylpropylenamine-oxime) is taken up by the brain soon after intravenous injection [7]. Soon after, the molecule undergoes a change rendering it less lipophilic, and it is trapped in the brain. The distribution of HMPAO thus reflects rCBF [243].

550 MBq (technetium 99m) hexamethyl propylene amine oxime (HMPAO; Amersham International, Amersham, UK) were injected intravenously under resting conditions with eyes open in a dimly lit, quiet room. Images were acquired 15 minutes later using a large field of view gamma camera (IGE 400T; IGE Medical, Radlett, UK or Sophy DS7; Sophy medical, Buc, France) with high resolution collimator and 360 degree rotation. 64 views of 20 seconds each were acquired onto a 64 x 64 matrix ("step and shoot"). Reconstruction, using a Hamming-Hann filter, was carried out in 3 planes with slices packed in pairs and viewed with 10% background subtraction.

Initially the presence of focally reduced perfusion was determined by qualitative visual assessment and subsequently confirmed by quantitative analysis of axial images. The hippocampal counts, however, were assessed using coronal images. Cortical regions (i.e. high frontal, parietal, frontal, temporal, posterior temporal, hippocampal and occipital) were identified with the help of an atlas [9]. The acquired images were compared with the atlas for the purpose of defining three particular anatomical levels, two in the axial plane and one in the coronal plane. The coronal slice was compared with the atlas in order to demonstrate the medial temporal structures.

Figure 2.1. Magnetic resonance imaging in DAT (coronal views). Top scan shows isolated right hippocampal atrophy with preservation of neocortex in a patient with minimal DAT. Bottom scan shows bilateral hippocampal atrophy and diffuse cortical atrophy in a patient with more established DAT.



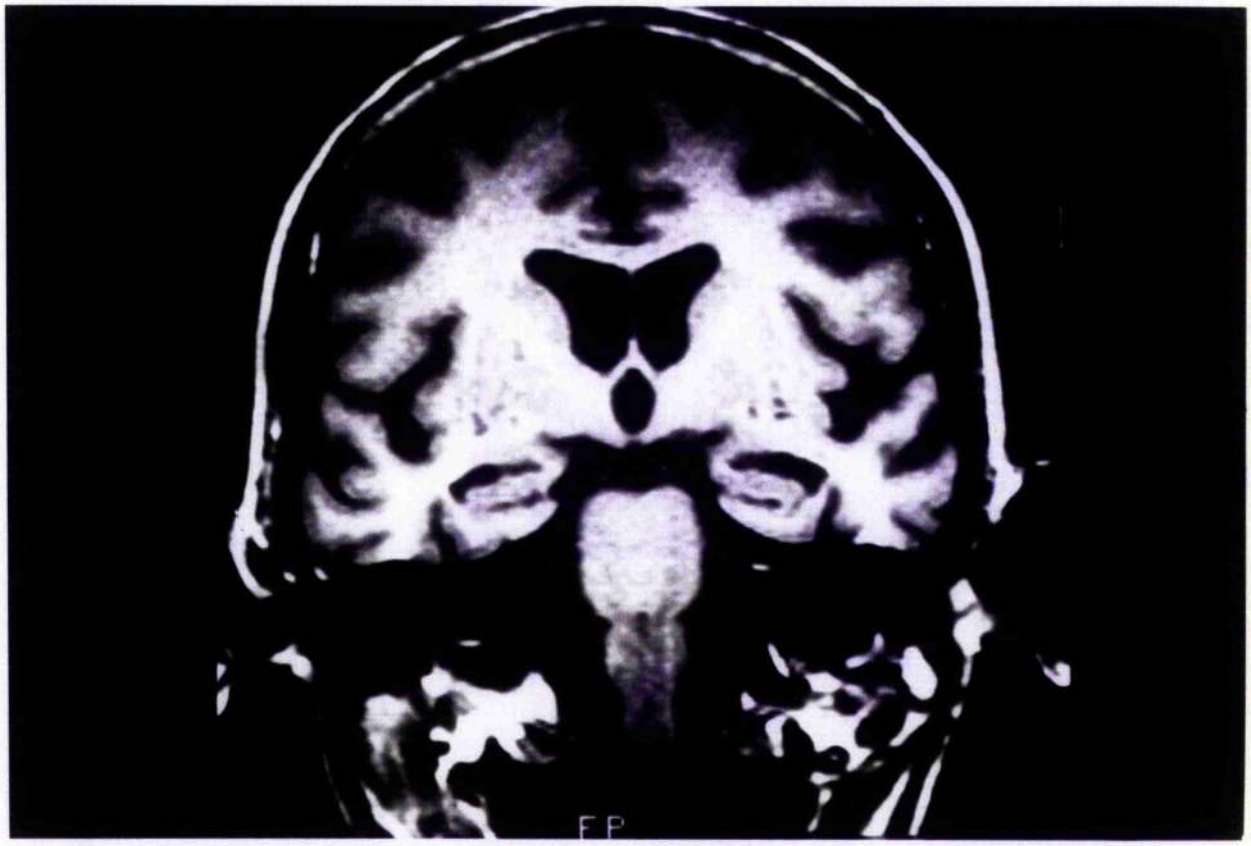
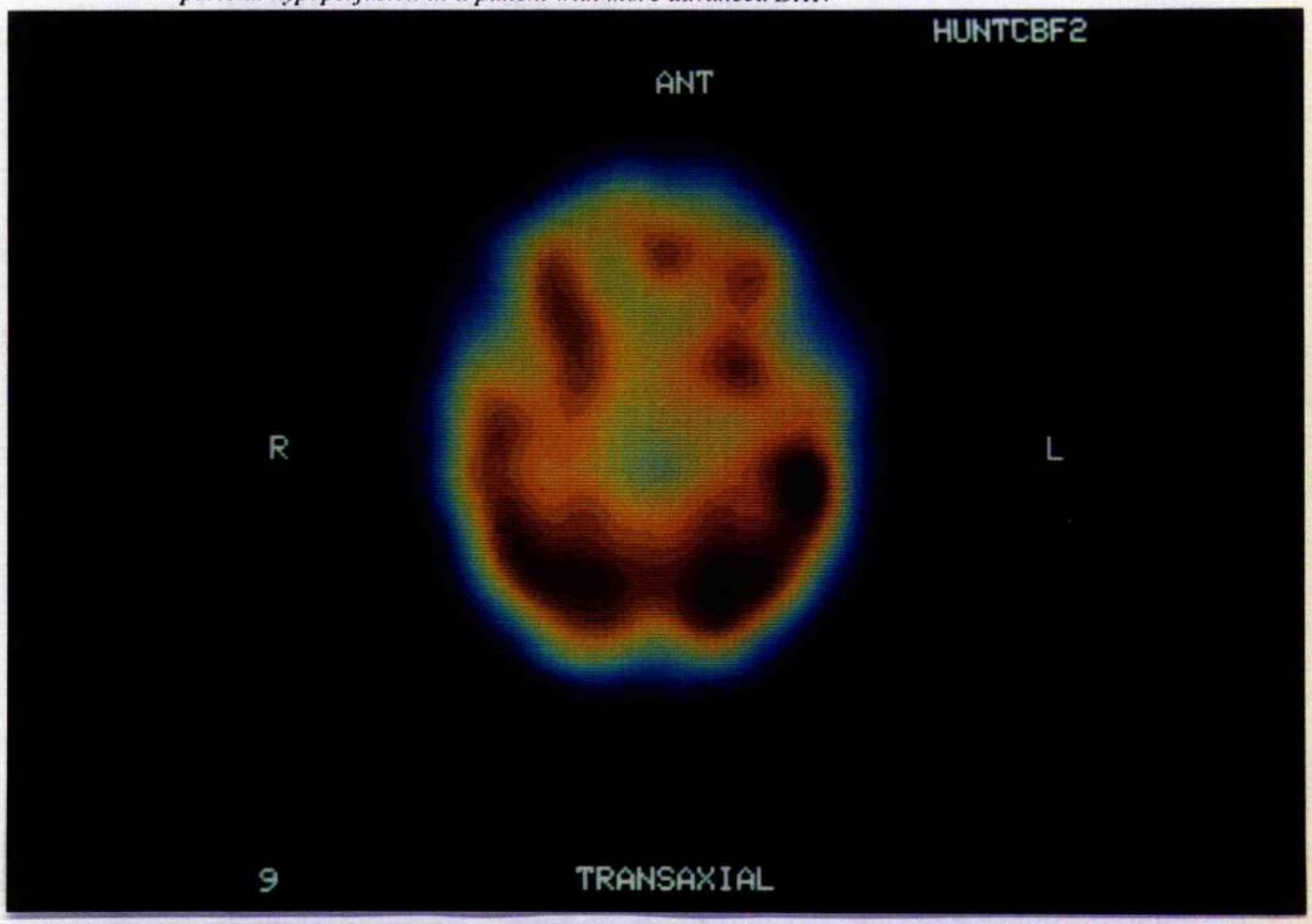


Figure 2.2. SPECT imaging in DAT (axial views). Top scan shows right medial temporal hypoperfusion in a patient with minimal DAT. Bottom scan shows bilateral temporo-parietal hypoperfusion in a patient with more advanced DAT.



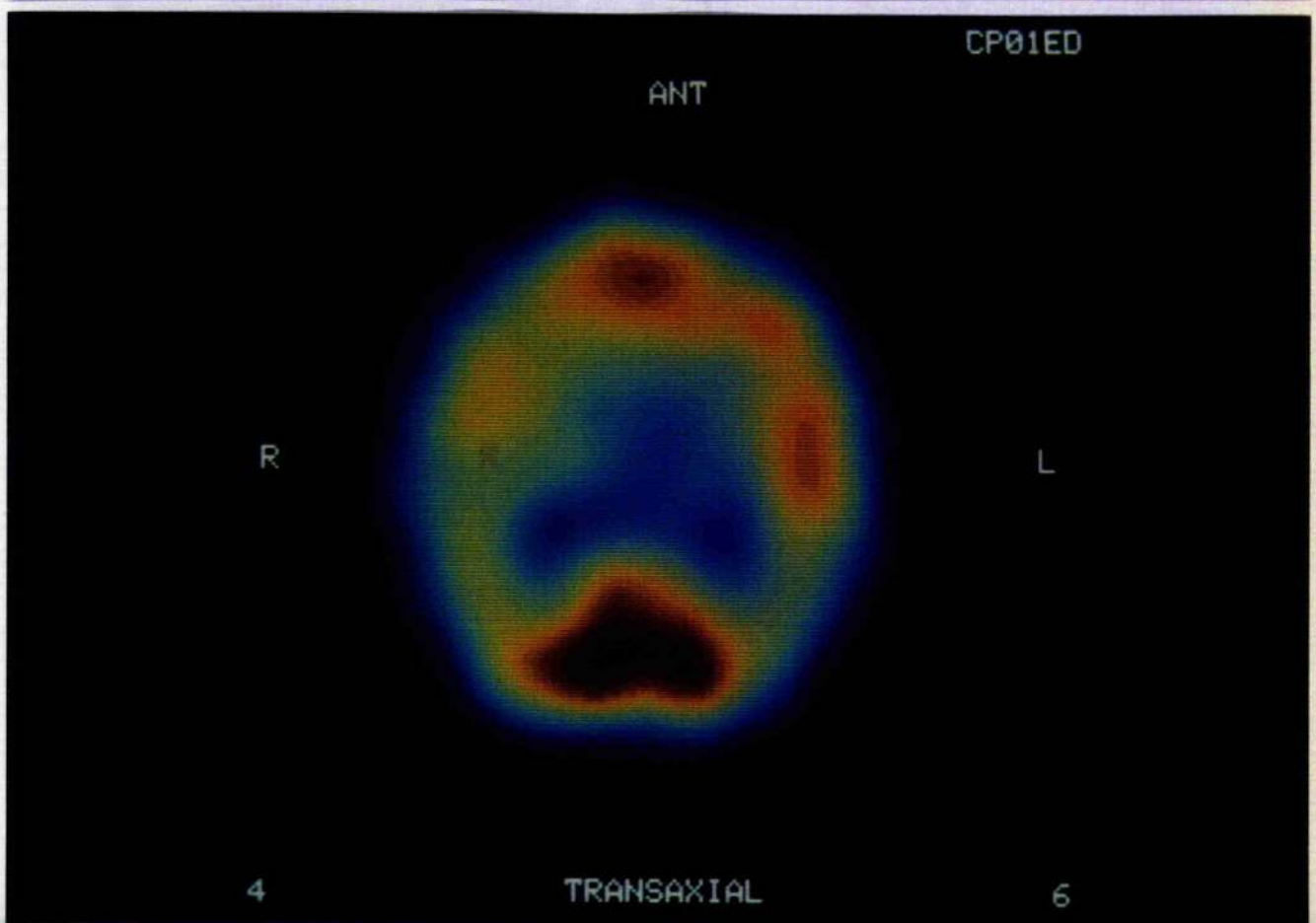
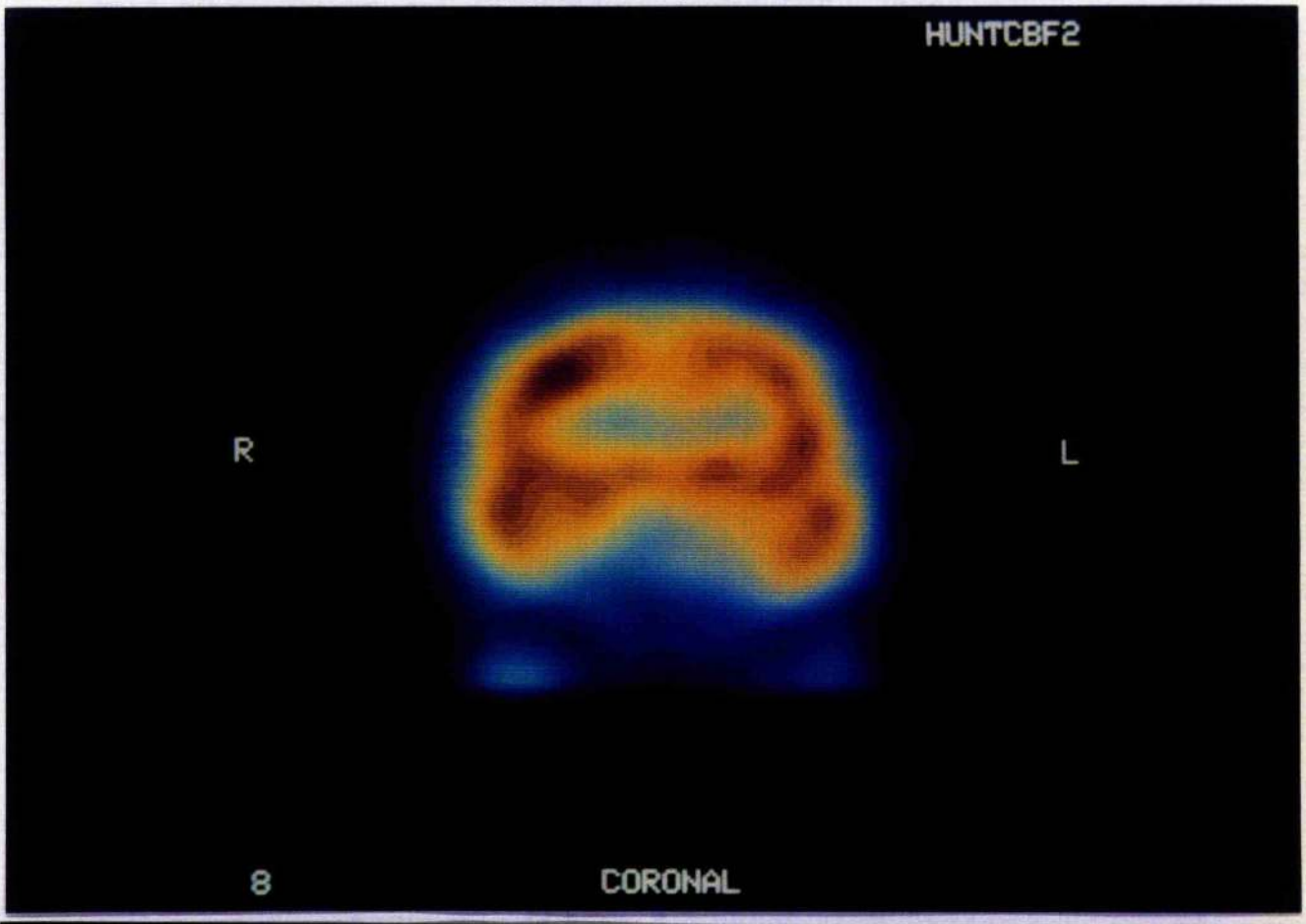
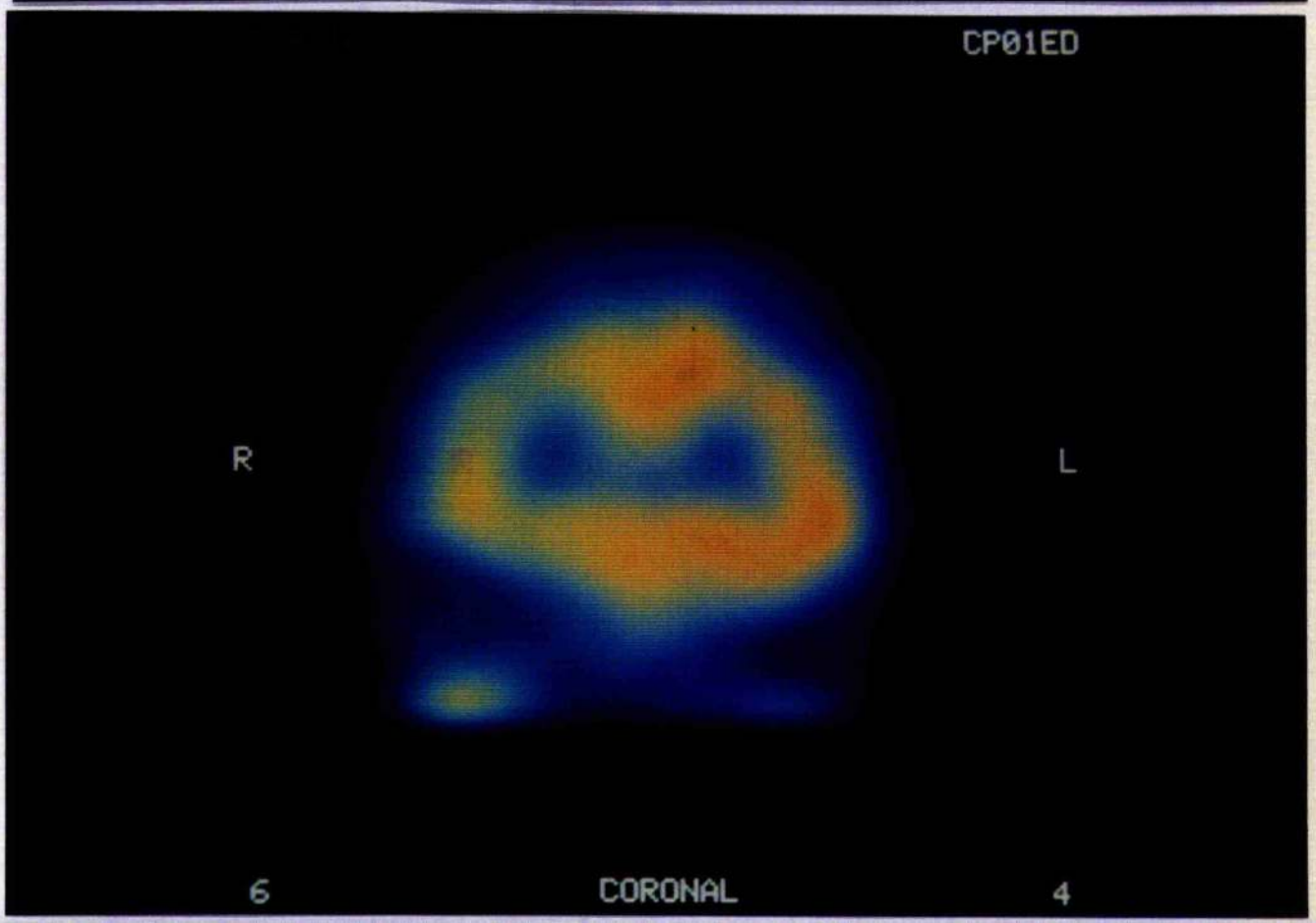


Figure 2.3. SPECT imaging in DAT (coronal views). Top scan shows isolated right medial temporal hypoperfusion in a patient with minimal DAT. Bottom scan shows bilateral medial temporal and global cortical hypoperfusion in a patient with more advanced DAT.

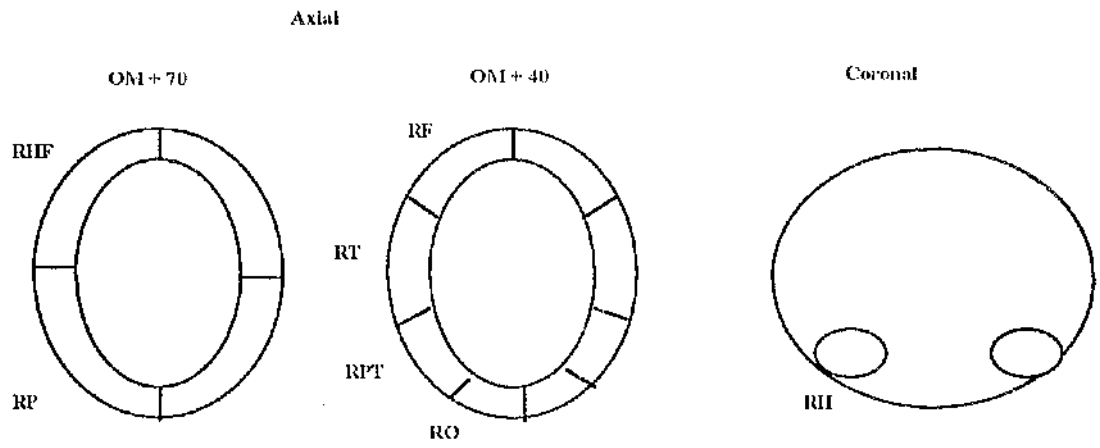




Regions of interest

Using the scanner's computer system, 14 regions of interest (ROI) outlining different brain regions were drawn on each of the slices, 4 on the high axial slice, 8 on the standard slice and 2 on the coronal slice. This was based on the work of Montaldi *et al* [230].

Figure 2.4. Diagrammatic representation of Regions of Interest (ROI) on SPECT images, for high axial, standard axial and coronal views



Key	
RHF	right high frontal
RP	right parietal
RF	right frontal
RT	right temporal
RPT	right posterior temporal
RO	right occipital
RH	right hippocampal
OM + 70	70mm superior to orbitomeatal line
OM + 40	40 mm superior to orbitomeatal line

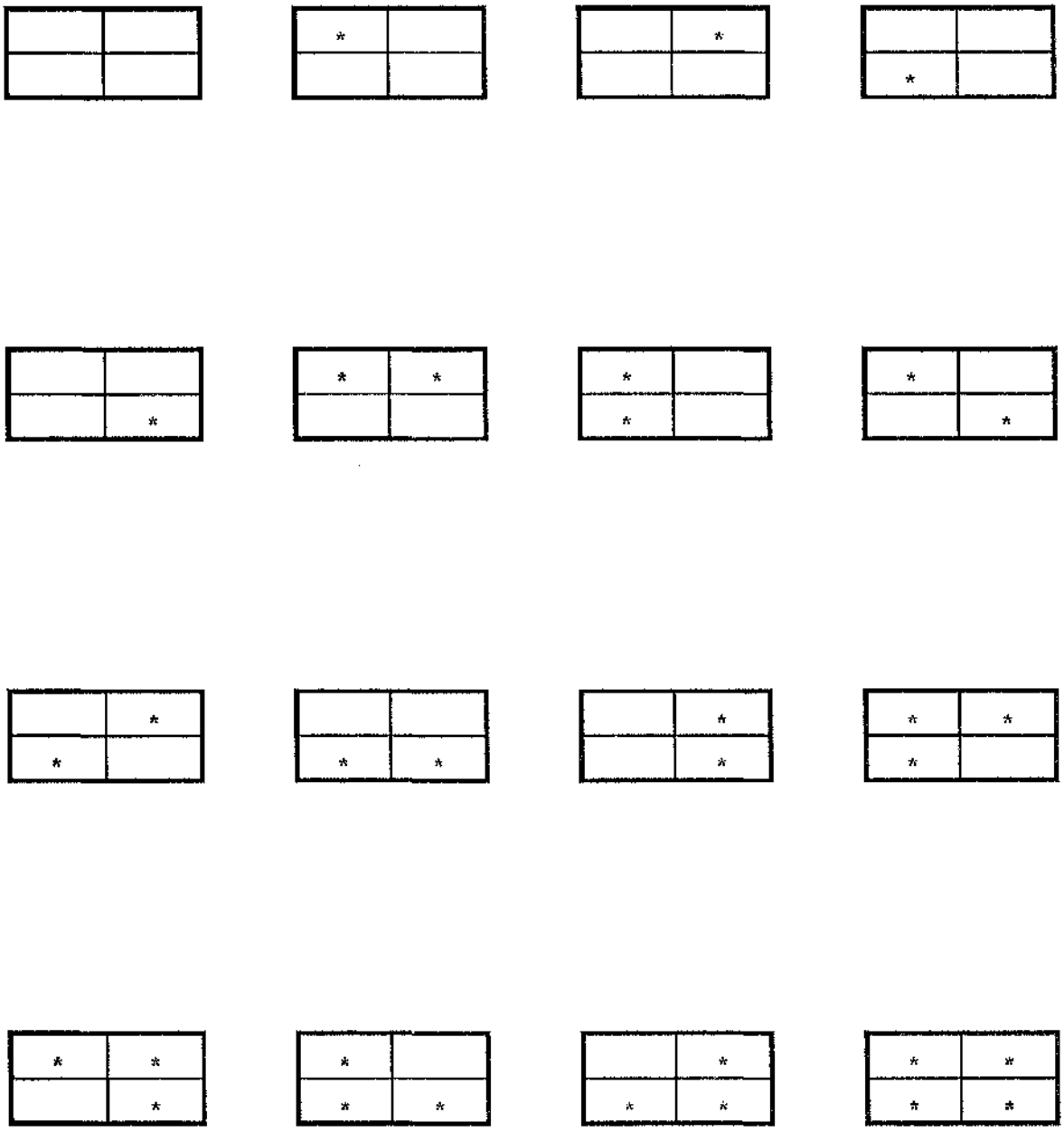
Corresponding right and left regions were symmetrically identical. The ROI boundaries were drawn along the outside surfaces of the brain and internally followed the division between the "grey" and "white" matter. On the standard slice the four regions were defined as frontal, temporal, posterior temporal and occipital; with high frontal and parietal on the high slice. On the coronal slice medial temporal regions were defined. For each region the area and mean number of counts per pixel were measured and expressed as a number of counts per unit area, i.e. a mean count density. To normalise these data I divided the mean count density for each ROI by the average rCBF of the occipital regions therefore producing an ROI/occipital activity ratio. Occipital rather than cerebellar regional cerebral blood flow was used for

standardisation. This is because the occiput is relatively spared in DAT, whether assessed by regional cerebral blood flow [97, 230, 272] or pathology [48], while cerebellar blood flow may be impaired due to crossed cerebellar diaschisis resulting from damage to the cortico-ponto-cerebellar system [20]. Admittedly, the choice of reference region in quantitative analysis of SPECT data is controversial, and others have found the cerebellum to be of greater use [321, 342].

Individual rCBF patterns

I also wished to study the pattern of regional hypoperfusion in DAT, and to address the controversy regarding whether DAT causes a predictable pattern of rCBF changes (i.e. initially temporo-parietal hypoperfusion, followed by frontal changes in more advanced disease). Using the method described by Waldemar *et al* [340] four brain regions were defined: a left and a right frontal region and a left and a right posterior region, in which rCBF was characterised as either normal or reduced. High frontal and frontal regions were used to define the anterior areas. If rCBF in each of these areas was normal, then anterior blood flow was said to be normal. Conversely, if rCBF in either of the regions was abnormal, then anterior rCBF was taken as being abnormal. Temporal, posterior temporal, parietal and hippocampal rCBF were used to obtain a measure of posterior rCBF. Using the above rCBF data, each patient was reclassified into one of 16 possible patterns.

Figure 2.5. Possible rCBF patterns in the patients with probable Alzheimer's disease.



Key

LF	RF
LP	RP

LF left frontal

LP left posterior

RF right frontal

RP right posterior

Statistical analyses

As many of the questions in this thesis employ statistical techniques, a brief account of the various means of statistical analysis will be given here.

Descriptive statistics

Usually, raw data will be shown. However, it is often desirable to describe the relative position of an observation within a distribution. One way of doing this is to calculate its standard score. This score, sometimes called the Z score, indicates how many standard deviations above or below the mean an observation falls. It is calculated by finding the difference between the value of a particular observation X_i and the mean of the distribution X, and then dividing this difference by the standard deviation S:

$$Z_i=(X_i-X)/S$$

The mean of Z scores is 0, and the standard deviation is 1. When the distribution of a variable is approximately normal and the mean and variance are known and are estimated from large samples, the Z score of an observation provides more specific information about its location. A Z score of -1.96 or lower, indicates performance below that of 95% of the control population.

Unpaired comparisons

This allows comparisons made between the average measurements of two groups.

Correlation and Covariance

Correlation is the degree of linear relationship between two variables.

Covariance is used to calculate how much changes in one variable affect the values of the other variables. It is possible to remove the effect of age, education etc. by covariance, and thereby study the correlation between two variables, having allowed for the effect of age, education etc.

Regression

Regression analysis explains or predicts the value of a dependent variable from one or more independent variables. In regression modelling, the predictors are independent variables; they predict the dependent variable. Regression modelling is useful when there is a linear relationship between the independent and dependent variables, when all observations are independent of each other. The portion of the dependent variable not explained by the independent variables is due to random error that follows a normal distribution with a constant variance.

In stepwise regression analysis, a model selection procedure helps choose the independent variables that are most useful in explaining or predicting the dependent variable.

Analysis of Variance (ANOVA)

An ANOVA studies the effect of independent variables on a continuous dependent variable when the independent variables are nominal rather than continuous. ANOVA determines the significance of the effects in a model by calculating how much of the variability in the dependent variable can be explained by the effect in question. If ANOVA indicates a group effect, then post hoc comparisons using Student-Newman-Keuls are applied to determine the origin of the group effect.

In a repeated measures design, there are two types of variables. A between factor distinguishes the characteristics of the subjects in the experiment. A within factor represents the different conditions under which each subject is measured.

Contingency Tables

Contingency table analyses determine whether a relationship exists between two nominal variables. A contingency table is a two-way tabular arrangement in which observations are categorised into one group for each of two nominal (grouping) variables.

In a Chi-Square test, the contingency table is studied to see which combinations of groups have more of fewer observations than would be expected if the two variables were independent. This can be done comparing the contingency table (observed frequencies) to the expected tables value, or by examining a table of post hoc cell contributions to the overall chi-square statistic.

Nonparametrics

Nonparametric statistics test hypotheses about data for which the underlying distribution of the data is not assumed. Rather than estimate the parameters of a hypothesised distribution, then perform a computation on these estimates (parametric statistics), nonparametrics employ alternatives such as sequentially ranking observations from all groups or variables of interest or comparing two groups observation-by-observation to test hypotheses. The Mann-Whitney U-test, the Kruskall-Wallis test and the Freidman test are the nonparametric equivalents of the unpaired t-test, one-way ANOVA and two-way ANOVA respectively.

Factor Analysis

Factor analysis reduces a large number of correlated variables to a smaller, more manageable number of factors. A factor is a linear combination of related variables that can take the place of the original variables in further analysis. The structure of the factors (the variables represented by each factor) is the most important information resulting from a factor analysis. Factor analysis is useful when one has many

correlated measurements for each of the experimental units, and one wants to concentrate on a smaller number of values than the number of measurements at hand, or one wants to learn about the interrelationships among the variables. This technique is known as dimensionality reduction.

The results of a factor analysis are summarised by a primary pattern matrix. For each factor, the entries in this matrix represent the coefficients (often called loadings) of the linear combination of the original variables that define that factor. The factor pattern matrix is then transformed by one or more transformations or rotations. The rotation helps one see the structure of the matrix more clearly by transforming it so that, for a given factor, as many variables as possible have either large coefficients or coefficients near zero. Then knowledge of the dataset is used to assign meanings to the factors that were extracted.

Discriminant Analysis

Discriminant analysis aims to classify cases into one of several mutually exclusive groups on the basis of a set of observed characteristics. Linear discriminant analysis does allow direct prediction of group membership, but the assumption of multivariate normality of the independent variables, as well as equal variance-covariance matrices in the two groups, is required for the prediction rule to be optimal.

Logistic Regression Analysis

This is a multivariate technique for estimating the probability that an event occurs. This model requires far fewer assumptions than discriminant analysis; and even when the assumptions required for discriminant analysis are satisfied, logistic regression still performs well. This directly estimates the probability of an event occurring.

Ethics

As this thesis involved the use of patients for neuropsychological testing and SPECT scanning, ethical approval was sought from the Local Research Ethics Committee, and was granted. Informed consent was obtained from the patient. A copy of the patient information sheet is included in the Appendix.

This study involved the use of SPECT scanning, which utilises radioactive material. This research was covered by a certificate issued by the Administration of Radioactive Substances Advisory Committee (ARSAC) of the Department of Health, to Dr K Miles, Consultant in Nuclear Medicine.

Chapter Three

Identification of Famous Faces and Famous Names in early Alzheimer's disease: Relationship to anterograde episodic and general semantic memory

Introduction

Remote memory or retrograde memory refers to memories occurring prior to the onset of pathology. The term may apply to autobiographical memory, or to memory for famous people and events. Here I am concerned with the latter.

In contrast to the extensive investigations of anterograde memory in DAT, remote memory has been investigated much less extensively [for review see [140]]. Although there is no doubt that patients with DAT show impairment on a range of remote memory tests including naming and identification of famous faces [25, 148, 360] or famous scenes [188, 280], a number of important clinical and theoretical questions remain unanswered. Firstly, there is the question of whether patients with DAT show a preservation of more distant memories (i.e. a temporal gradient). Second, is the issue of how early in the course of the disease deficits in remote memory can be detected, and hence the relationship of the remote memory to anterograde memory impairment. Third, is the nature of the deficit in terms of contemporary cognitive models; if, as a prior study has suggested [148], the defect in the identification of famous people reflects a loss of semantic memory, is this related to the more general loss of semantic knowledge found in patients with DAT ? I shall now consider each of these questions in more detail.

Is remote memory impaired in DAT and, if so, is there a temporal gradient?

Most studies of remote memory in DAT have concentrated, almost exclusively, on the issue of whether patients with DAT show a temporal gradient on tests of remote memory. This is of theoretical interest because considerable controversy has surrounded the interpretation of the temporal gradient found in patients with alcoholic Korsakoff's syndrome ([3, 57, 68, 188, 209, 221, 294, 311] but for counter example see [286]). Some investigators have attempted to explain the latter on the basis of the defect in laying down (or encoding) new memories during the 20 or more years of alcohol abuse that typically precede the onset of the amnesic syndrome (see [2, 68]). According to this hypothesis, the pattern of extensive and temporally-graded loss is regarded as a consequence of the chronic alcoholism and not as an intrinsic part of the amnesia. Other authors have argued that the temporally-graded pattern is a direct result of the acute diencephalic damage that occurs in Korsakoff's syndrome since the same pattern can be observed in patients with thalamic infarction [141, 206] and in transient global amnesia [150]. More recently, a two-factor model has been adopted by some investigators [57, 188]; by this account, one factor is the effect of long-term alcohol, so that alcoholics retain somewhat less information each year, due to their well documented chronic learning deficit. The second factor is a loss, or lack of access to, old memories, that appears acutely as a result of diencephalic damage. The latter results in a selective deficit in recalling episodic memories. Butters and Cermak [57]

built on the earlier suggestion by Cermak [64] that newly acquired knowledge may be episodic in nature, but with time and continued rehearsal the memories become independent of specific temporal and spatial contexts, and thus acquire the characteristics of semantic memories. Because of this controversy, it is of interest to know whether patients with other forms of brain pathology can show a temporal gradient.

To date, studies in DAT have produced somewhat conflicting findings. While Wilson *et al* [360], using a famous faces test, found no temporal gradient, Beatty *et al* [25] using a similar task did find better performance on items from more distant decades. Studies by Sagar *et al* [280] and by Kopelman [188], both using a pictorial scenes test, found impairment on recall and recognition of famous events, but only recall showed a temporal gradient. These studies clearly suggest that recall- and recognition-based remote memory may show distinct patterns of performance and that the finding of a temporal gradient, or not, is likely to depend upon the method of testing subjects. In an attempt to settle this question, Hodges *et al* [148] analysed recognition, identification (i.e. the ability to provide detailed information even if items are unnamed), and naming with and without cueing. In contrast to the aforementioned studies, Hodges *et al* found impairment in all test conditions, with a temporal gradient for recognition and identification of famous faces, but not for naming. It should be pointed out, however, that the degree of sparing of distant memories was at most modest and did not approach the degree seen in patients with Korsakoff's syndrome. One aspect that has not been adequately considered in these studies has been the potential confounding effect of the slowly developing anterograde memory impairment in DAT. It is likely that anterograde episodic memory has been deteriorating for a number of years by the time patients present with sufficient memory and cognitive deficits to be classified as probable cases of DAT.

How early in the course of DAT is remote memory impaired ?

This leads on to the second unresolved question of how early in the course of the disease remote memory deficits can be detected, and the related issue of how consistent such deficits are across patients with mild DAT. As mentioned above, it is now well established that the vast majority of DAT patients present with memory failure, although very occasional histologically proven DAT cases with predominant language [123, 259] or visuo-perceptual [36, 199] deficits have also been reported. Impairment on delayed recall of verbal material is an almost universal manifestation of their impaired episodic memory [352, 353]. This finding reflects the fact that the earliest neuropathological changes can be found in the hippocampal-related structures, most notably the transentorhinal region [42, 159]. The transentorhinal region is a complex transitional zone located between the entorhinal region proper and the

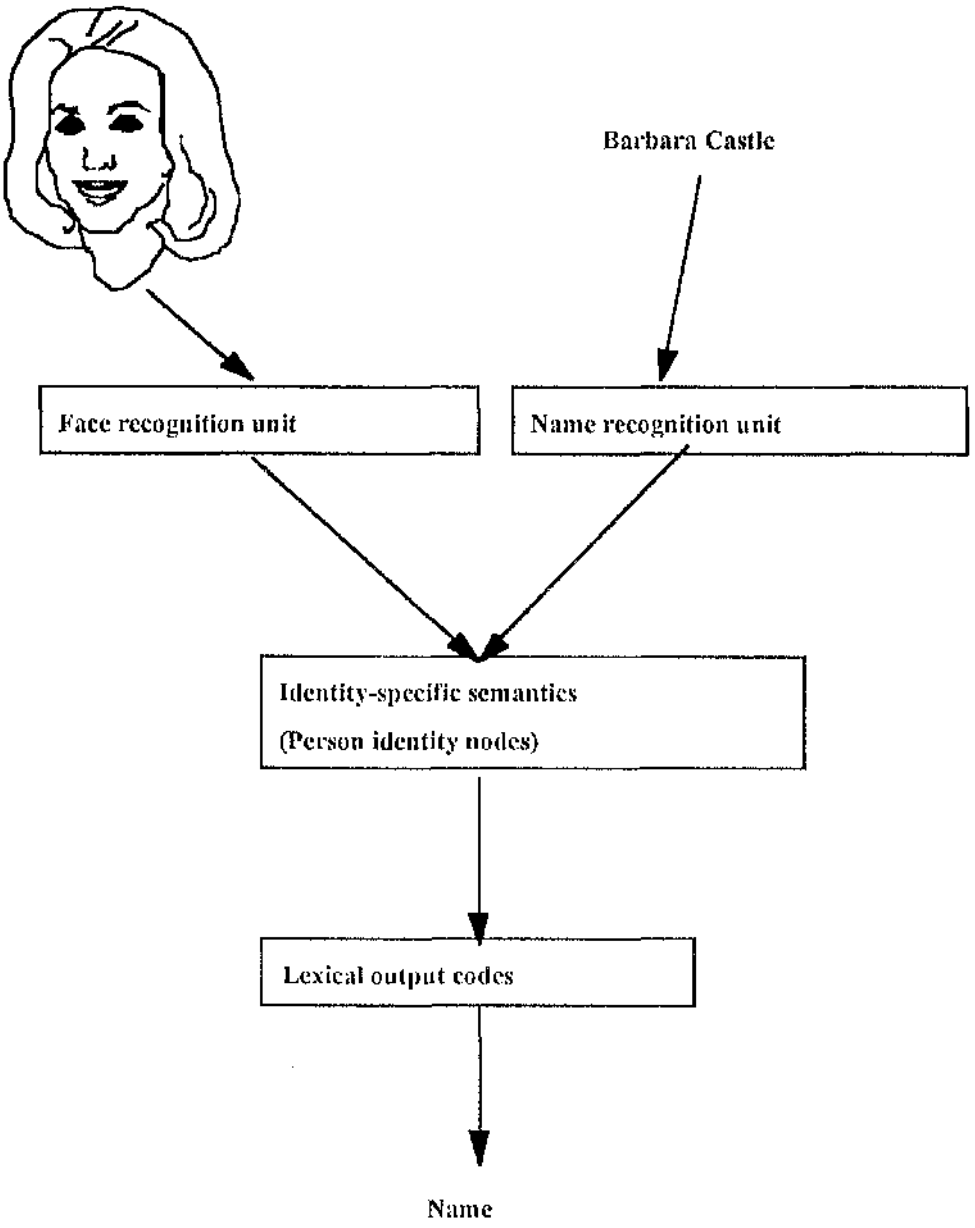
adjoining temporal isocortex. Lesions in this region are critically placed to disrupt connections to and from the hippocampal formation and would thus be expected to produce severe impairment in episodic memory, of the type found in early DAT. On the basis of the study of amnesic patients with anoxic damage, confined to either the hippocampus *per se* or involving additional hippocampal-related structures, Squire [308] has suggested that pure hippocampal pathology causes an isolated anterograde amnesia, but as soon as other surrounding structures are involved there is inevitably a combined anterograde-retrograde amnesia. To date, all studies of remote memory in DAT have involved patients with well established disease. Moreover, they have considered the groups' mean performance only, rather than considering individuals within the group. Based on the distribution of pathology in DAT, I postulate that the majority, if not all, patients should exhibit both anterograde and retrograde memory deficits from very early in the course of the disease. However, the locus of pathology is unlikely to be absolutely identical in all patients and it is possible that some patients may present with a pure anterograde amnesic syndrome.

What is the nature of the cognitive deficit ?

The third issue is the nature of the cognitive deficit underlying the remote memory impairment in DAT. Although it has been shown that patients with DAT fail on tests involving the naming of famous faces or scenes [25, 148, 188, 280, 360], the nature of the deficit has been addressed only very recently [148]. As a starting point to their study, Hodges *et al* [148] took the information-processing model of face identification first proposed by Bruce and Young [47](see Figure 3.1). In this model, face recognition, identification and naming involve a sequence of discrete cognitive processes. First, structural encoding of the perceptual features provides a visual description of the seen face. Recognition of the face as familiar proceeds by comparing this to the store of known familiar faces (or face recognition units). The next stage consists of accessing person-specific semantic knowledge. Naming requires the additional activation of phonological name codes. Patients may show breakdown at any level and the failure to name a picture of a famous person may, therefore, reflect an impairment at any level of this process. Hodges *et al* analysed recognition of famous faces from amongst non-famous foils, identification (i.e. the ability to provide specific information about un-named faces) and naming, with and without semantic and phonological (first name) cues. Their DAT group were impaired on all components, but showed relative preservation of recognition and naming with first name cues. They argued that the impairment was due primarily to loss of person-specific semantic knowledge and that pre- and post-semantic processes remain relatively spared in DAT. It should be noted that none of the patients in the Hodges *et al* study had very mild disease, no attempt was made to compare performance on

this test with performance on anterograde memory or traditional semantic memory tasks, and only group data were considered.

Figure 3.1. Model of face and name processing, based on Bruce and Young model of face processing, and Burton and Bruce model of name processing



More recently, the Bruce and Young model has been extended to encompass the processing of famous names [52, 53, 333]. It has been postulated that name

recognition requires the activation of a name recognition unit, which is similar to, but separate from, the corresponding face recognition unit [47, 364]. Identification proceeds by activating person-specific semantic knowledge, the latter stage being common to face and name processing.

Famous name recognition and identification have not been studied in patients with DAT. Based on the study by Hodges *et al* [148], I would predict that recognition of famous names should be relatively preserved in DAT and that identification, which requires access to semantic information, should be impaired. Furthermore, the degree to which impairment on either face or name recognition predicts performance on the other gives a measure of their functional, and presumably anatomical, association. By contrast, if a common semantic system is disrupted, there should be significant concordance between face and name identification.

How is memory for public figures related to semantic memory?

The final issue concerns the relationship between performance on famous person-based remote memory tests and general tests of semantic memory. It is now well established that patients with DAT show progressive disruption of semantic memory [65, 66, 143, 149, 213]. If it is confirmed that the failure to name and identify famous persons also reflects a loss of person-specific semantic knowledge then it is clearly of interest to ask the question of whether performance on general tests of semantic memory correlates with performance on famous face and name tests. A lack of correlation clearly implies that stores of person-specific and object-related general knowledge may dissociate and thus presumably have separate neural bases. The neural basis of semantic memory in general remains rather poorly defined although there is converging evidence to suggest that the temporal neocortex, particularly the left infero-lateral region, plays a central role [82, 256]. Even less is known about the localisation of person-specific semantic knowledge (or person identity nodes in the model discussed above [333]); three separate case studies of patients with loss of person-based semantic memory have all implicated the right temporal lobe [101, 103, 128]. Thus, the neurological evidence supports the contention that general and person-based semantic knowledge may be separately represented.

Aims

The aims of this component of the study were to establish whether memory for famous faces and names is impaired in patients with very early DAT. More specifically, I wished to address these issues:

i) do patients with DAT show a preservation on more distant memories (i.e., a temporal gradient)?

ii) Is remote memory universally impaired early in the course of the disease and what is the relationship of the remote memory to anterograde episodic memory impairment? and

iii) Is the defect in the identification of famous people due to a loss of person-specific semantic memory (with relative sparing of face and name recognition), and, if so, is this related to the more general loss of semantic knowledge found in patients with DAT?

Methods

Subject groups

Data collected from the 33 DAT patients and 30 controls tested at year 1 were used in this Chapter.

Tests

The tests employed are described in Chapter 2.

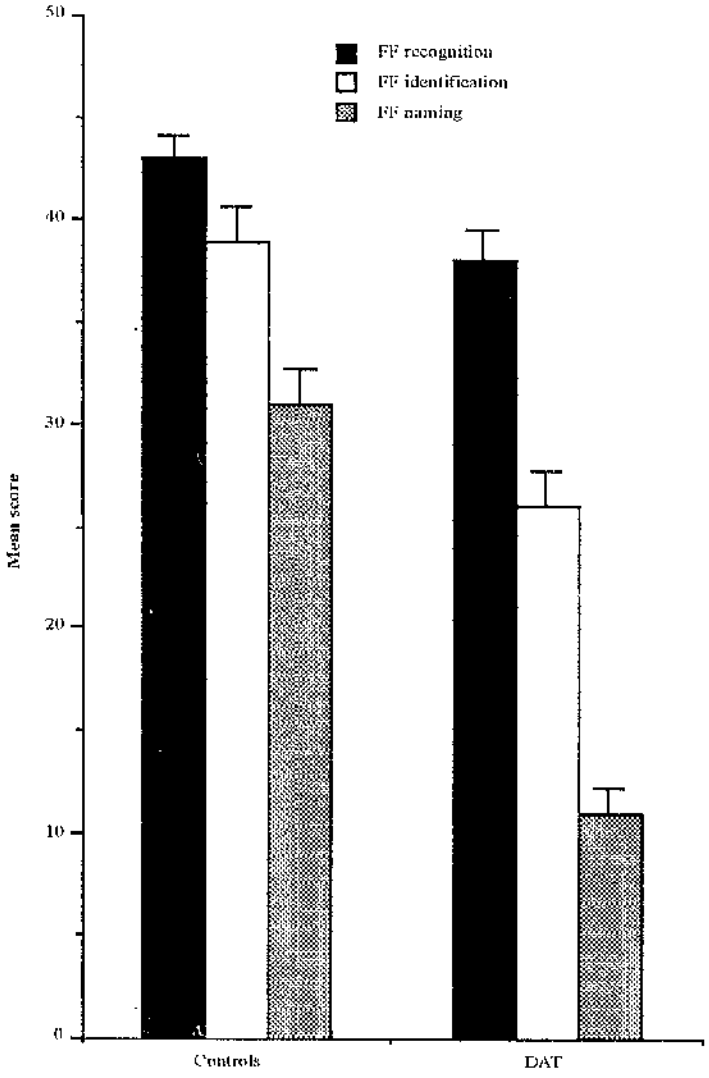
Results

Is remote memory impaired in DAT ?

Effect of DAT on recognition, naming and identification of famous faces

Figure 3.2 represents the overall mean scores for the DAT patients and normal controls for recognition, identification and naming. Two by three ANOVA showed that recognition, identification and naming were all significantly lower in the DAT group than the controls group (t [d.f. 61]=2.5, $p<0.05$; t [d.f. 61]=5.6, $p<0.0001$; t [d.f. 61]=9.5, $p<0.0001$, respectively). On account of possible ceiling effects leading to a not normal distribution, I subsequently performed nonparametric analysis using Mann-Whitney U-tests. The same results were obtained.

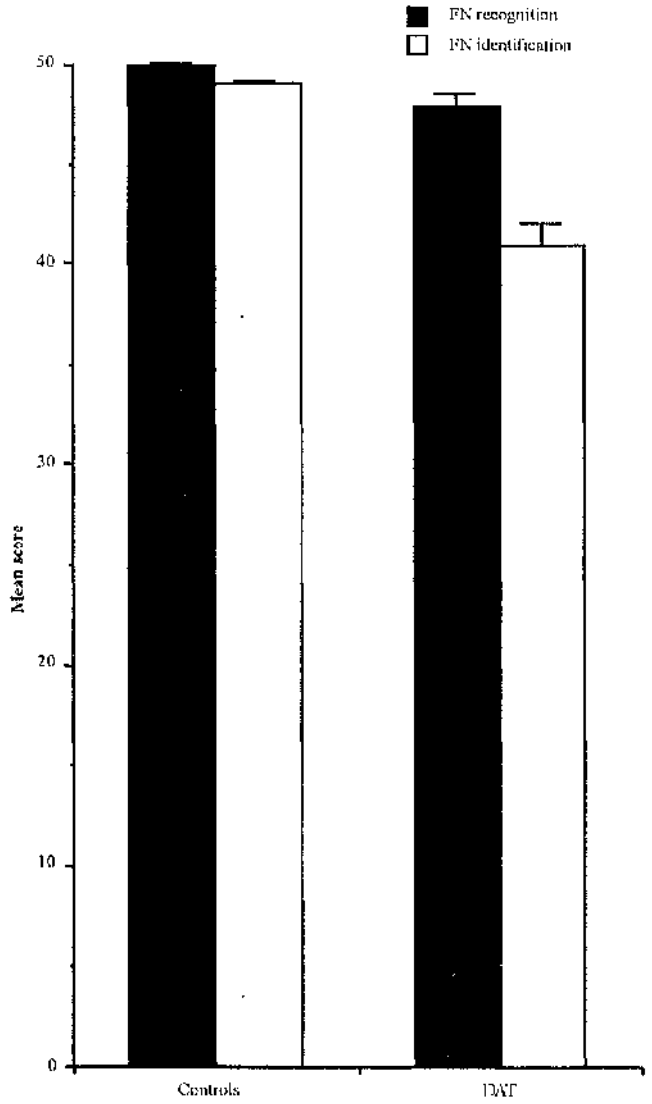
Figure 3.2. Overall performance on the Famous Faces Test by controls (n=30) and DAT patients (n=33) showing mean scores (with standard error of the mean) for recognition, identification and naming. Differences for face recognition, identification and naming were highly significant.



Effect of DAT on recognition and identification of famous names

Figure 3.3 represents the overall mean scores for the DAT patients and normal controls for recognition and identification. The DAT group's mean scores were significantly lower than controls in both conditions (t [d.f. 61]=2.9, $p<0.01$; t [d.f. 61]=7.1, $p<0.0001$, respectively). Nonparametric Mann-Whitney U-tests confirmed these results.

Figure 3.3. Overall performance on the Famous Names Test by controls (n=30) and DAT patients (n=33) showing mean scores (with standard error of the mean) for recognition and identification. Differences for name recognition and identification were highly significant.



Is there a temporal gradient ?

The data were also analysed according to the decade of the photographs for each of the test conditions.

Famous faces

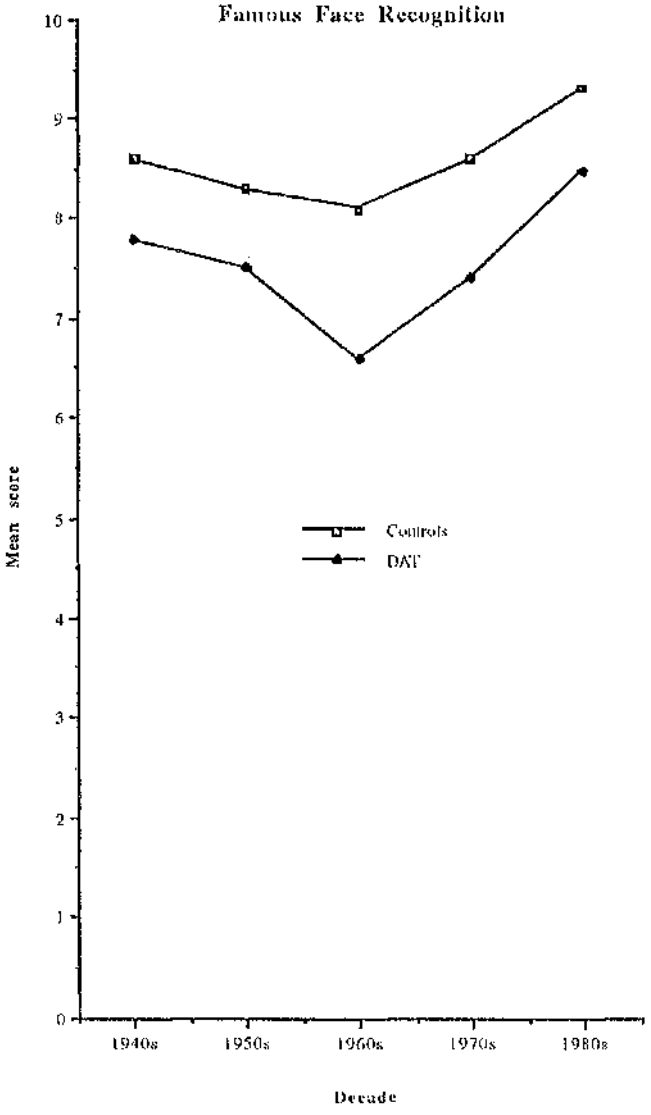
Recognition: Figure 3.4 compares the mean scores per decade for the DAT patients and normal controls for face recognition. A 2 (groups) X 5 (decades) repeated measures ANOVA of the recognition scores revealed significant group ($F(1,61)=6.3$, $p<0.05$) and decade effects ($F(4,244)=19.5$, $p<0.0001$) but no significant interaction ($F(4,244)=1.5$, $p>0.05$).

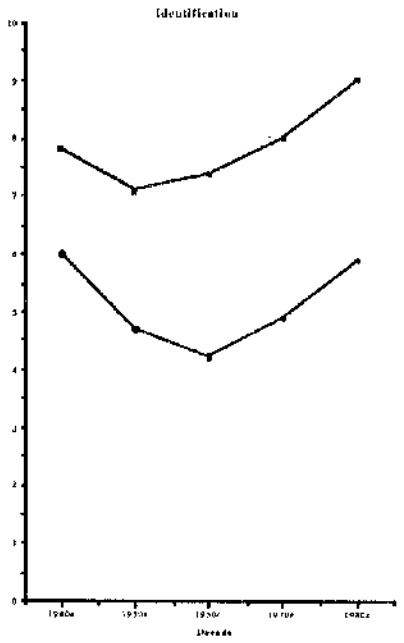
Identification: For identification, a repeated measures ANOVA produced highly significant group ($F(1,61)=31.3$, $p<0.0001$) and decade effects ($F(4,244)=21.1$, $p<0.0001$) as well as a significant group by decade interaction ($F(4,244)=3.5$, $p<0.01$). Post hoc pairwise analysis by Student-Newman-Keuls tests for pair-wise differences showed that controls performed significantly better on the 1980s faces than on all other decades ($p<0.05$), except the 1940s. In DAT patients, however, this decade effect was lost, showing that DAT patients were more impaired at identification of recently famous faces.

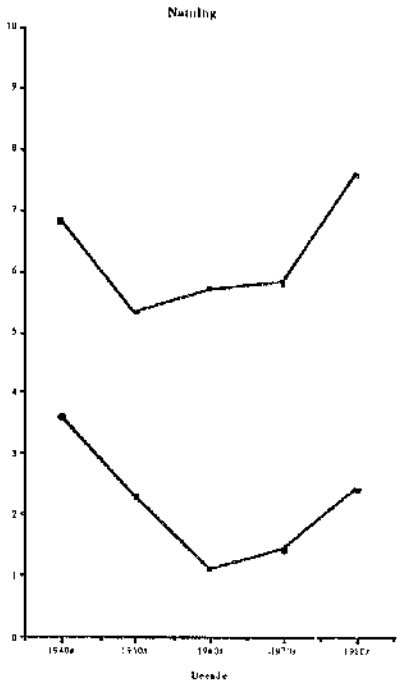
Naming: For naming, a 2X5 ANOVA produced highly significant group ($F(1,61)=94.0$, $p<0.0001$) and decade effects ($F(4,244)=23.2$, $p<0.0001$)(see Figure 3.4). There was also a significant group by decade interaction ($F(4,244)=7.0$, $p<0.0001$). Post hoc analysis again showed that controls performed significantly better on the 1980s faces than on all the other decades with the exception of the 1940s. By contrast, the DAT subjects performed significantly better on the faces from the 1940s than on the faces from all other decades ($p<0.05$). These findings suggest that there is a slight temporal gradient in the famous face naming by DAT patients, with relatively worse performance on recent decades, but (as I shall discuss below) this may simply reflect the insidious onset of anterograde memory deficits over a ten-year period.

As can be seen from Figure 3.4, controls performed more poorly on famous faces from the 1950s, 1960s and 1970s than from the 1940s and 1980s for recognition, identification and naming, presumably due to my selection of relatively easier faces from the latter two decades. This U-shaped function seen in controls was also present in the DAT patient group. There was, however, a significant interaction between subject group and decade: DAT patients are impaired with respect to controls particularly for recent decades. Although statistically significant, the degree of temporal gradient, illustrated in Figure 3.4, is at most very mild, quite unlike the marked temporal gradient seen in the Korsakoff's syndrome.

Figure 3.4. Temporal pattern of the DAT patients (n=33) and normal controls (n=30) on the Famous Faces Test in the three test conditions: recognition, identification (i.e. accurate description of person represented) and naming. Significant group differences were present for recognition, identification and naming. Positive interactions, indicating a temporal gradient, were present for recognition, identification and naming.







Famous names

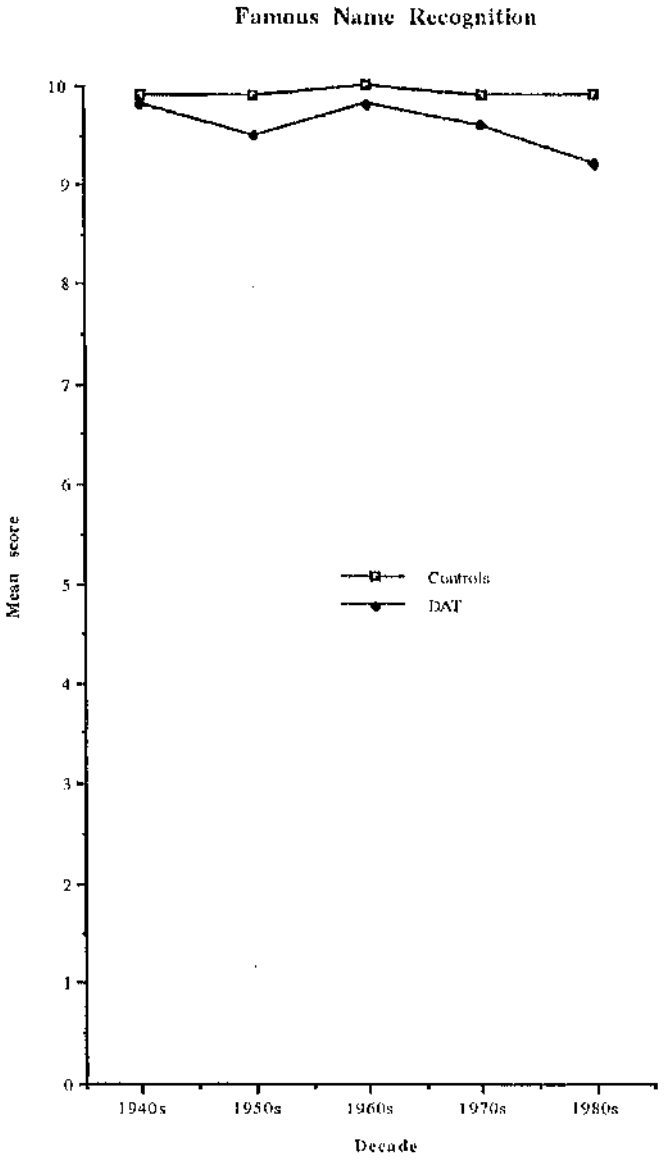
Figure 3.5 compares the mean scores per decade for the DAT patients and normal controls for famous name recognition. For name recognition, a 2X5 ANOVA produced highly significant group ($F(1,61)=8.4$, $p<0.005$) and decade effects ($F(4,244)=5.2$, $p<0.001$) as well as a significant group by decade interaction ($F(4,244)=4.0$, $p<0.005$). Post hoc analysis of the controls' data showed that they performed equally well for each decade. DAT patients, by contrast, showed a significantly impaired performance for names from the 1980s with respect to the 1940s and 1950s ($p<0.05$), indicating a statistically significant, but minimal, temporal gradient.

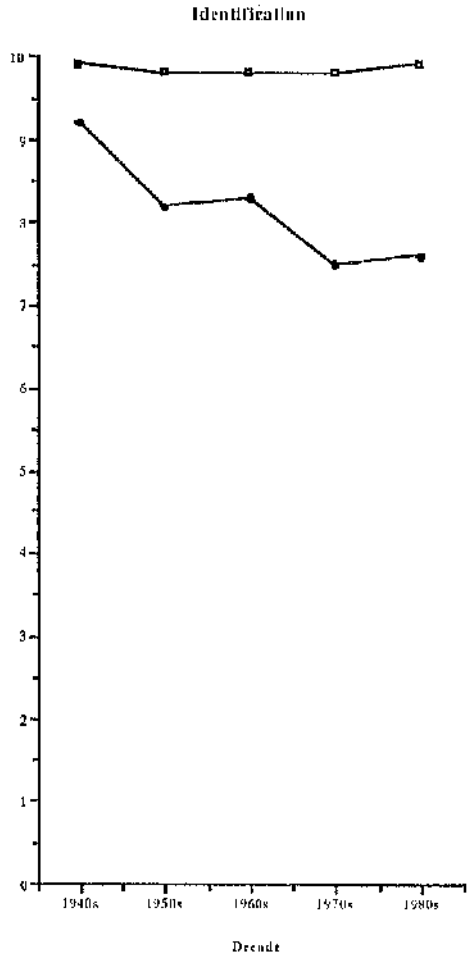
For name identification, a 2X5 ANOVA produced highly significant group ($F(1,61)=50.0$, $p<0.0001$) and decade ($F(4,244)=11.6$, $p<0.0001$) effects (see Figure 3.5) as well as a significant group by decade interaction ($F(4,244)=9.2$, $p<0.0001$). Post hoc comparisons showed that controls performed equally well across the decades. DAT patients, by contrast, performed better on 1940s names compared to all subsequent decades ($p<0.05$). Also, their performance on 1950s names was significantly better than those from the 1970s and 1980s ($p<0.05$).

Again the finding of a statistically significant group by decade interaction should be interpreted with caution due to the near ceiling performance of controls.

In conclusion, I found evidence of a very gentle temporal gradient on both the Faces and Names Tests, in keeping with previous studies which have produced conflicting results regarding the presence or absence of such a gradient.

Figure 3.5. Temporal pattern of the DAT patients' (n=33) and normal control subjects' (n=30) performance on the Famous Names Test in the two test conditions: recognition and identification (i.e. accurate description of person represented). Significant group differences were present for both conditions. Positive interactions, indicating a temporal gradient, were present for both recognition and identification.





How early in the course of DAT is remote memory impaired ?

Figures 3.6 and 3.7 show the performance of the individual DAT patients on the famous faces and names tests, with the cut-off level being taken as the 10th centile for controls. The patients have been ordered by level of global cognitive performance as judged by their performance on the MMSE. Twenty-five of the 33 patients (76%) performed above the 10th centile for controls on famous face recognition. Corresponding figures for face identification and naming were twelve of the DAT patients (36%) and three (9%), respectively. Three DAT patients (9%) performed normally on all three components of the famous face test (recognition, identification and naming). Nineteen (58%) were above the 10th centile for name recognition and

three (9%) were above this for name identification. Three DAT patients (9%) performed above the 10th centile for both name recognition and identification. Only one DAT patient (3%) scored above the 10th centile for all components of the faces and names tests.

It can be seen from Figures 3.6 and 3.7 that there was no obvious relationship between remote memory performance and severity of dementia. A correlational analysis, as seen in Table 3.1, confirmed the lack of significant correlation between any of the remote memory measures and severity of dementia as measured by the MMSE. To study this relationship further, the five components of remote memory were entered into a stepwise regression analysis to predict dementia severity as measured by the MMSE. Together the five tests could predict only 21% of the variance in MMSE scores. Thus, there was a very poor association between severity of dementia and extent of remote memory impairment.

Table 3.1. Correlations between public memory, anterograde and semantic memory for DAT patients

	LMI	LMD	CRI	CRg	VeRI	ViRg	ViRI	VeRg	FFR	FFN	FFI	FNR	FNI	CFlu	Nam	W-P	N to D	PPTT	MMSE
LMI	1.00																		
LMD	0.68*	1.00																	
CRI	0.39	0.29	1.00																
CRg	0.21	0.12	0.38	1.00															
VeRI	0.55*	0.60*	0.52*	0.07	1.00														
ViRg	0.38	0.22	0.47*	0.22	0.27	1.00													
ViRI	0.54*	0.44	0.58*	0.18	0.34	0.55∂	1.00												
VeRg	0.57*	0.35	0.44	0.19	0.36	0.61∂	0.49*	1.00											
FFR	0.04	0.10	0.00	0.21	-0.22	0.44	0.19	0.38	1.00										
FFN	0.08	-0.12	0.07	0.15	-0.06	0.40	0.12	0.33	0.54∂	1.00									
FFI	0.15	0.08	0.02	0.13	-0.12	0.48	0.16	0.34	0.82∂	0.77∂	1.00								
FNR	0.24	0.06	-0.18	-0.02	0.06	0.17	-0.11	-0.02	0.18	0.30	0.41	1.00							
FNI	0.39	0.12	0.11	0.28	0.15	0.38	0.15	0.24	0.40	0.49*	0.65∂	0.79∂	1.00						
CFlu	0.47*	0.10	0.51	0.21	0.31	0.28	0.36	0.37	-0.11	-0.10	-0.08	0.04	0.24	1.00					
Nam	0.27	0.03	0.25	-0.06	0.27	0.16	0.21	0.35	-0.04	0.07	0.06	0.21	0.42	0.59∂	1.00				
W-P	0.28	0.14	-0.32	-0.21	0.09	0.12	-0.09	0.19	0.18	0.17	0.39	0.70∂	0.59∂	0.13	0.47ß	1.00			
N to D	0.31	-0.06	0.21	0.17	0.15	0.23	0.11	0.38	-0.04	0.00	0.11	0.37	0.51*	0.61∂	0.69∂	0.44	1.00		
PPTT	0.32	0.13	0.39	0.30	0.19	0.35	0.26	0.34	0.02	-0.05	0.04	0.10	0.42	0.61∂	0.50∂	0.06	0.63∂	1.00	
MMSE	0.50*	0.22	0.30	0.43	0.26	0.43	0.42	0.44ß	-0.13	-0.26	-0.1	0.09	0.17	0.50*	0.42	0.18	0.51*	0.49*	1.00

ß p<0.01
∂ p<0.001

Key

LMI	Logical memory immediate recall	FFN	Famous face naming
LMD	Logical memory delayed recall	FFI	Famous face identification
CRI	CERAD delayed recall	FNR	Famous name recognition
CRg	CERAD delayed recognition	FNI	Famous name identification
VeRI	Doors & People verbal recall	CFlu	Category fluency
ViRg	Doors & People visual recognition	Nam	Picture naming
ViRI	Doors & People visual recall	W-P	Word-picture matching
VeRg	Doors & People verbal recognition	N to D	Naming to description
FFR	Famous face recognition	PPTT	Pyramids and Palm Trees Test

Figure 3.6. Performance on famous face measures by each DAT patient ordered according to worsening dementia severity from left to right, with 10th centile for controls marked by horizontal line

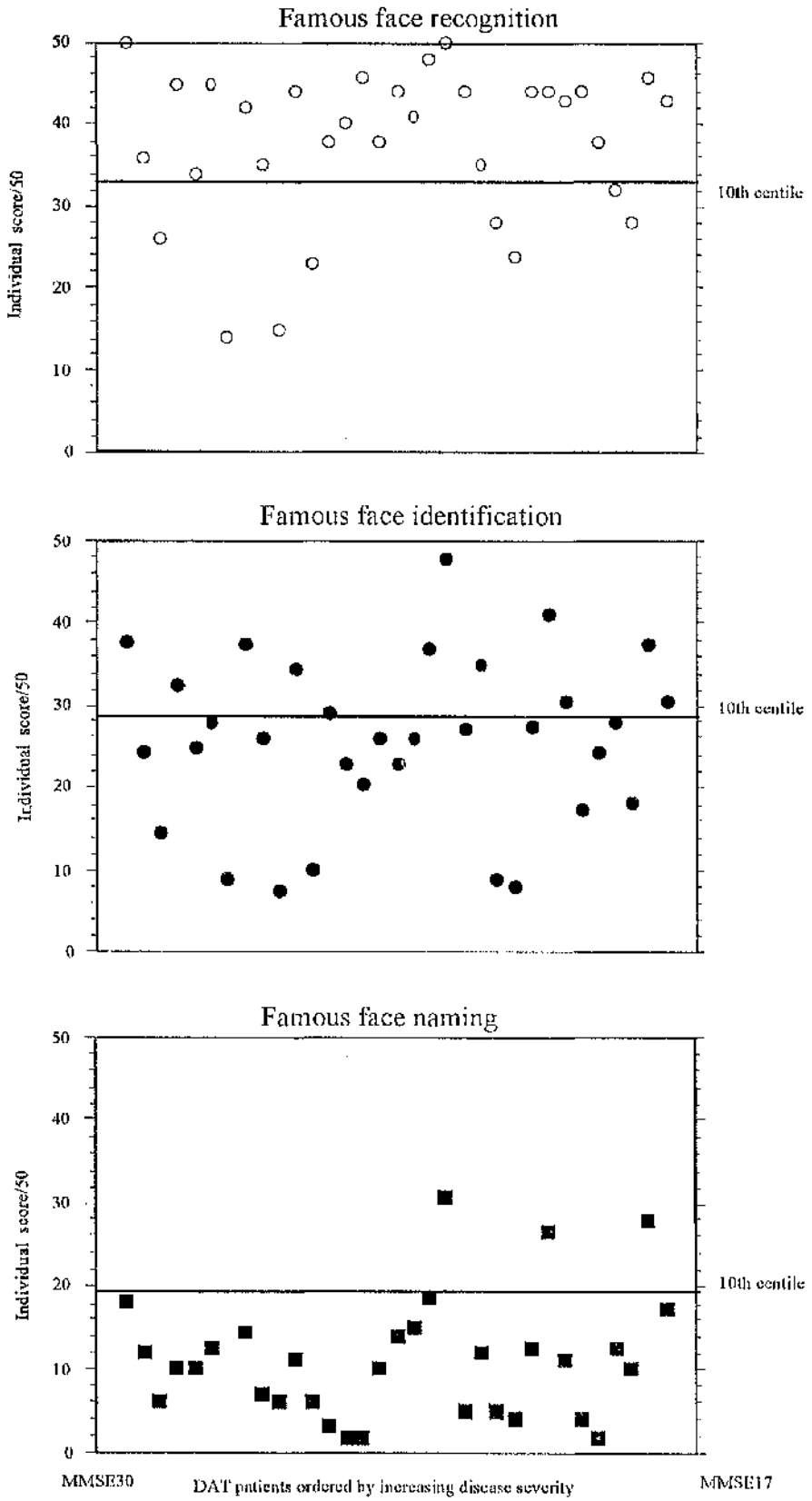
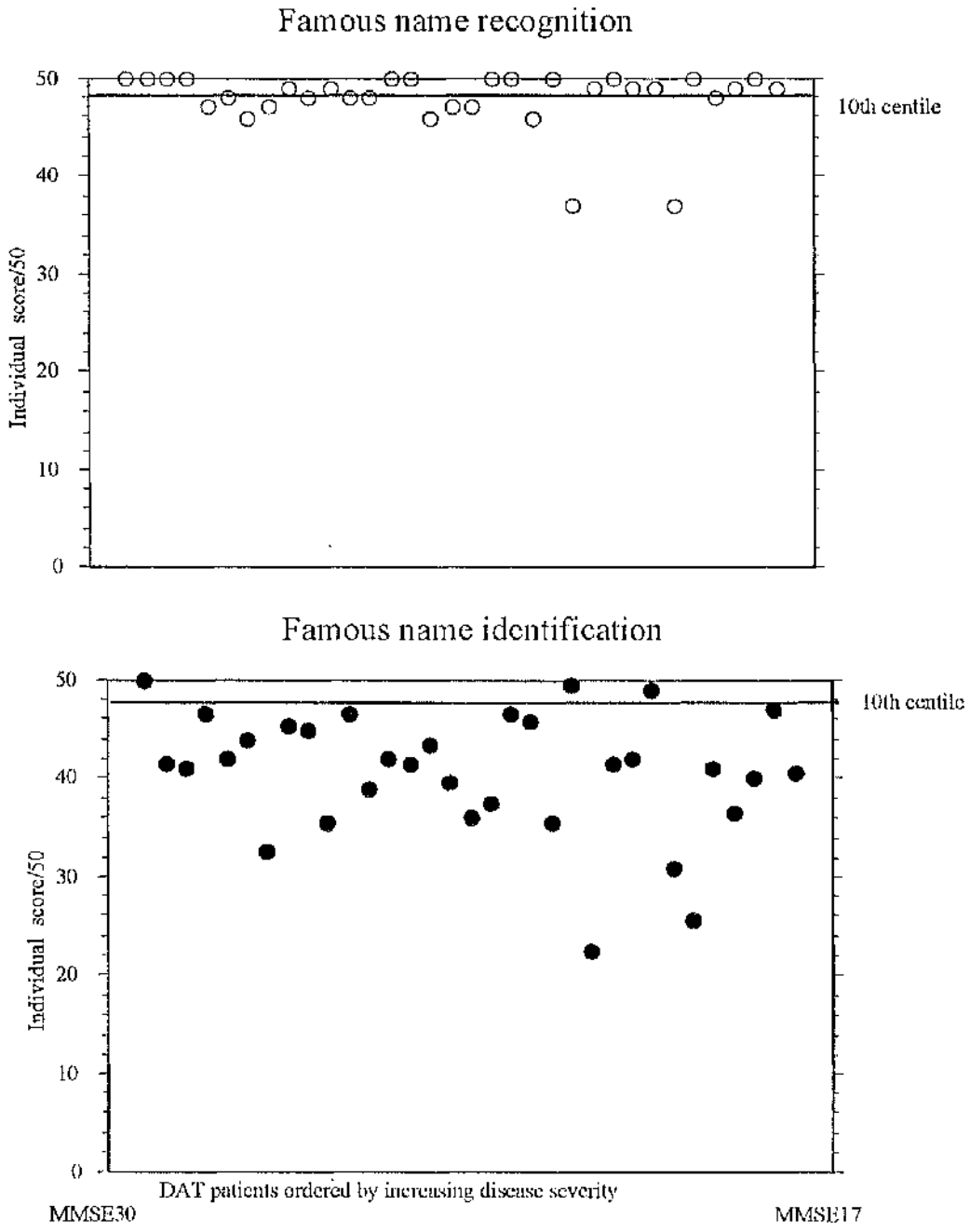


Figure 3.7. Performance on famous name measures by each DAT patient ordered according to worsening dementia severity from left to right, with 10th centile for controls marked by horizontal line



Three conclusions can be reached from these analyses. First, remote memory is impaired in the majority of cases with even early DAT. Second, there is considerable heterogeneity within the DAT cases which suggests that there may be different patterns of evolution of the cognitive deficit in DAT. Third, there is a very poor association between remote memory impairment and the severity of dementia as judged by the MMSE.

What is the correlation between remote and anterograde memory ?

As shown in Table 3.2, the DAT patients were significantly impaired (t[d.f. 61] range = 5.6-13.6, p<0.0001) on all measures of anterograde episodic memory: the logical memory component of the WMS-R, the CERAD word list, and the Doors and People Test of verbal and visual recall and recognition. These anterograde episodic memory results are discussed further in Chapter 6.

Table 3.2. Performance of the controls and DAT patients on the three measures of anterograde memory - showing mean scores (SD)

		Maximum score	Controls n=30	DAT group n=33	p-values
Logical memory	Immediate	47	9.9 (2.8)	3.9 (2.2)	<0.0001
	Delayed	47	8.8 (3.0)	0.9 (1.5)	<0.0001
CERAD	Immediate recall	10	7.6 (1.3)	3.7 (1.7)	
	Delayed recall	10	6.7 (1.7)	1.2 (1.5)	<0.0001
	Delayed recognition	10	9.7 (0.5)	7.3 (1.6)	<0.0001
Doors & People	D&P verbal recall	12	8.9 (2.9)	4.1 (1.0)	<0.0001
	D&P verbal recognition	12	9.7 (3.4)	5.0 (2.5)	<0.0001
	D&P visual recall	12	10.1 (4.5)	4.1 (2.6)	<0.0001
	D&P visual recognition	12	9.1 (3.4)	4.9 (2.5)	<0.0001

I addressed the association between anterograde and remote memory firstly by means of a correlation analysis, as shown in Table 3.1. Because of the number of comparisons, only r-values with $p<0.01$ were considered as significant. It can be seen that there was a poor correlation between anterograde and remote memory performance. I also addressed this relationship by entering the anterograde data as independent variables into a stepwise regression analysis to predict identification of both famous faces and famous names. Performance on all anterograde measures predicted 31% of the variance in famous face identification, but only 16% of the variance in famous name identification. This adds further evidence to the finding of a poor association between anterograde and retrograde memory.

An alternative means of exploring the relationship was by factor analysis. Eighteen key variables were included in the analysis. The method employed was a Varimax rotation applied to the entire data set. Three factors were extracted with eigenvalues above 1.00 (eigenvalues = 10.0, 2.1, 1.4). Table 3.3 gives the mean factor loadings for the 18 key variables. Only those variables loading above 0.50 are reported. The most parsimonious interpretation of the factor structure is that Factor 1 represents anterograde and semantic memory, Factor 2 represents famous name performance and some semantic measures, and Factor 3 represents famous face performance.

Table 3.3. Summary of loadings for remote, episodic and semantic tests of factors 1-3 following principal components factor analysis

	Factor 1	Factor 2	Factor 3
Logical memory - immediate	0.74		
Logical memory - delayed	0.76		
CERAD immediate recall	0.85		
CERAD delayed recall	0.87		
CERAD recognition	0.80		
D&P verbal recall	0.72		
D&P nonverbal recognition	0.74		
D&P nonverbal recall	0.74		
D&P verbal recognition	0.70		
Famous face recognition			0.90
Famous face identification			0.78
Famous name recognition		0.78	
Famous name identification		0.57	
Category fluency	0.75		
Naming	0.62		
Word-picture matching		0.85	
Naming to description	0.51	0.54	
Pyramids & Palm Trees Test	0.65		

What components of the face and name model are affected in DAT ?

Effect of disease on separate components of face processing

Identification/recognition: To see if the DAT patients identified a smaller proportion of the faces that they recognised than did the controls, I analysed the mean proportion of recognised faces that were subsequently identified by the group. The controls identified 91% of the faces they recognised as famous, while DAT patients identified 68%. A repeated measures ANOVA showed a group (controls vs DAT) effect ($F(1,61)=18.8$, $p<0.0001$), a condition (recognition vs identification) effect ($F(1,61)=163$, $p<0.0001$) and a group by condition interaction ($F(1,61)=42.6$, $p<0.0001$). This offers evidence that the deficit in DAT is predominantly at the semantic level and that the poor performance at identification is not simply an artefact produced by the DAT groups' lower face recognition score, although (as I discuss below) this difference should be interpreted with caution since recognition and identification employed different test strategies (i.e. forced-choice vs. free recall).

These findings also suggest that recognition and familiarity can occur independent of accessing semantic information.

Naming/identification: A similar analysis of the proportion of identified faces that were correctly named showed that DAT patients named a significantly smaller proportion of the faces that they identified (42%) than did controls (79%). Repeated measures ANOVA showed a group effect ($F(1,61)=62.1$, $p<0.0001$), a condition (identification vs naming) effect ($F(1,61)=258$, $p<0.0001$) and a group by condition interaction ($F(1,61)=20.7$, $p<0.0001$). This finding implies that the poor naming performance is over and above the deficit in face identification score, and may be due to additional impairment at a post-semantic level of processing.

Effect of disease on separate components of name processing

Identification/recognition

To see if the DAT patients identified a smaller proportion of the names that they recognised than did the controls, I analysed the mean proportion of recognised names that were subsequently identified by the groups. DAT patients identified 80% of the names that they recognised, while controls identified 99% of the names they recognised. Repeated measures ANOVA showed highly significant effects of group ($F(1,61)=35.3$, $p<0.0001$) and condition ($F(1,61)=96.4$, $p<0.0001$) as well as a group by condition interaction ($F(1,61)=64.8$, $p<0.0001$). This shows that the impaired identification by DAT patients is not simply due to their impaired performance on recognition, but is due to loss of stored semantic knowledge of famous persons.

Association between cognitive subcomponents of face and name processing

The above results, with reference to Figure 3.1, suggest that all components of the face and name model are affected by DAT, i.e. face recognition units, name recognition units, semantic knowledge of famous people and the post-semantic lexicon. Valentine *et al*'s model [333] suggests that face and name recognition units are separable, but that accessing information about famous people from their faces or names draws on the same semantic store. If DAT pathology were to impair the neural substrate for this common semantic store, then I would expect performance on face and name identification to be strongly associated. By contrast, the model postulates that face and name recognition rely on functionally, and presumably, anatomically, separable modules. Thus DAT pathology may affect one, other or both, and I would consequently expect less of an association between face and name recognition.

My finding of a significant correlation between face and name identification ($r=0.79$, $p<0.001$) but not for face and name recognition ($r=0.18$, $p>0.05$), as seen in Table 3.1, suggests that face and name identification may draw upon a common store, in contrast to face and name recognition. However, it should be remembered that the

same 50 famous people were used in both tests. This allows one to analyse each patient's performance for each famous person, whether accessed by face or name. This offers a more powerful method for addressing the issue of the association between cognitive subcomponents of face and name processing.

Firstly, I analysed performance for identification of famous faces and famous names. For each famous face, for each subject, it was determined whether the face and name were correctly identified, whether both were not identified or whether only one was identified. These data were entered into a contingency table (see Table 3.4). An analysis of famous face and name identification showed that there was a highly significant association between them (corrected Chi Square = 163.9, $p<0.0001$). Examination of the data showed that the observed frequencies of either identifying both face and name, or not identifying both face and name, were higher than expected. Correctly identifying either face or name alone also occurred significantly less often than would occur by chance. This would suggest that there is a highly significant association between famous face and famous name identification, and is supportive of Valentine *et al*'s claim that face and name identification rely on a unitary store of semantic knowledge, rather than separate face and name knowledge.

A similar contingency analysis indicated that there was a significant association between face and name recognition (corrected Chi Square = 28.3, $p<0.0001$), although this was less marked than for the above analysis for identification. Examination of the cell contributions indicated that the observed frequency of recognising both face and name was higher than expected. Correctly recognising either the face or name alone also occurred significantly less often than would occur by chance. The significant association between famous face and famous name recognition suggests that face and name recognition units are not completely independent, but may be functionally linked.

Table 3.4. Comparison of famous face recognition and famous name recognition, of famous face identification and famous name identification, and of famous face identification and naming, for each famous person, in the 33 DAT patients

		Famous face recognition		
		impaired	normal	total
Famous name recognition	impaired	43	44	87
	normal	367	1196	1563
	total	410	1240	1650

If face correct, name correct 96%.
If name correct, face correct 76%.

		Famous face identification		
		impaired	normal	total
Famous name identification	impaired	304	60	364
	normal	567	719	1286
	total	871	779	1650

If face correct, name correct 92%.
If name correct, face correct 56%.

Is knowledge of famous people related to general semantic memory ?

It can be seen from Table 3.5 that the DAT patients were significantly impaired on all five measures of semantic memory (the category fluency, picture naming, word-picture matching and naming to description subtests of the Hodges *et al* [144] battery and the Pyramids and Palm Trees Test [153]).

Table 3.5. Performance of the controls and DAT patients on the five measures of semantic memory - showing mean scores (SD)

	Maximum score	Controls n=30	DAT group n=33	p-values
Category fluency	-	114.0(24.5)	73.9 (23.5)	<0.0001
Picture naming	48	48.0 (0.2)	41.0 (4.1)	<0.0001
Word-picture matching	48	48.0 (0.0)	46.9 (2.2)	<0.01
Naming to description	24	22.9 (1.0)	19.0 (3.8)	<0.0001
Pyramids & Palm Trees Test	52	52.0 (0.2)	49.0 (3.0)	<0.0001

To study the relationship between knowledge of famous people and general semantic memory, a correlational analysis was performed, as shown in Table 3.1. It can be seen that performance on famous names correlated significantly with some of the general semantic measures (word-picture matching and naming to description), but that there was *no* correlation between famous face performance and semantic memory measures. To address this issue further, a stepwise regression analysis using semantic tests as independent variables to predict famous face and famous name identification was carried out. Semantic memory tests predicted only 20% of the variance in famous face identification, but, by contrast, predicted 51% of the variance in famous name identification.

A principal components factor analysis, shown in Table 3.3, suggested that knowledge of famous persons accessed from photographs did not load in the same factor as general semantic measures. For knowledge accessed by names, this loaded in the same factor as the word-picture matching and naming to description tests of general semantic memory.

The results of both the stepwise regression and the principal components factor analysis suggest that memory of famous people, particularly when assessed by names, is associated with general semantic memory to a certain extent. By contrast, there seems to be little association between knowledge of famous people when accessed from faces, and general semantic memory.

Discussion

The results confirm that remote memory is impaired very early in the course of DAT. All components of the tests were impaired in the DAT patients as a group. Although analysis of group data showed the DAT group were impaired on tests of remote memory, examination of individual patients' data revealed considerable heterogeneity: some patients had quite impaired remote memory, while others had intact remote memory. These findings confirmed the presence of a very mild temporal gradient, but it was less marked than observed in previous studies. Applying a cognitive model of face and name processing to these data, it would appear that face recognition units, name recognition units, semantic and post-semantic processing are all affected by DAT. There was also evidence for the independence of general and person-specific semantic knowledge. I shall now address the three principal issues raised at the start of the chapter.

Is the retrograde amnesia of DAT temporally-graded ?

As already mentioned, the interpretation of the data with respect to the presence and degree of any temporal gradient was complicated by two factors. Firstly, the skewed distribution of the controls' scores, particularly their near ceiling performance on the

names test, leads one to view the results of the analysis of variance with caution. Secondly, the U-shaped function seen on the faces test, due to the better performance of controls on the very old (1940s) and very recent (1980s) faces, makes the temporal gradient less apparent visually although it is statistically significant. With these provisos, the results do suggest the presence of a very mild temporal gradient on remote memory, but the most striking finding was that patients, even early in the course of DAT, showed impairment which extended back over five decades. Superimposed upon this global deficit there was disproportionate impairment for the most recent decade. These two components require explanation. The cause of the global deficit will be explored more fully below; this reflects, I argue, a loss of semantic information about the famous persons represented. Regarding the superimposed temporal gradient, there are a number of possible interpretations. It has been suggested that the mild temporal gradient may be a reflection of the episodic memory impairment found in DAT. Butters and Cermak [57] claimed that newly acquired knowledge may be episodic in nature, but that with time and continued rehearsal, the memories lose their temporal and spatial contexts, and become more semantic in nature. Baddeley, by a similar argument, claims that all memories are initially episodic. Repeated episodic presentations of the same item leads to an overlaying effect, by which temporal and contextual tags become less necessary for retrieval, and the memory become semantic. By these accounts an impairment in anterograde and retrograde episodic memory would result in a temporally-graded retrograde amnesia. Thus the temporal gradient found in DAT may be a result of episodic impairment affecting memory for more recently famous faces; this is over and above the semantic memory loss which is responsible for the temporally extensive impairment.

A second possible explanation relates to gradually developing anterograde memory impairment. Post hoc analysis of patients' results shows that their performance differs from that of controls most on the 1980s personalities. The onset of DAT is notoriously insidious and it is possible, therefore, that the patients may have had subclinical disease for as long as a decade prior to clinical presentation. Their poor performance for the 1980s may represent an early anterograde impairment rather than being a true remote memory loss. Longitudinal assessment of the patient group should allow one to decide between these two explanations.

In this study there was evidence of a temporal gradient for naming of famous faces whereas the previous study by Hodges *et al* [148] did not find this pattern. This discrepancy is due, most likely, to the fact that in the current study the controls demonstrated a recency effect for famous face naming (i.e. better performance on 1980s faces); the previous study did not achieve this. The temporal gradient which was observed is even gentler than in other recent studies [188, 280] which might be

explained by the nature of the patient group. Half of the patients have MMSE scores above 24, conventionally taken as the cut-off for normal. Thus their episodic memory may be relatively mildly, rather than totally, defective, causing their performance on recently famous faces and names to be less impaired than in other studies.

How early in the course of the disease is retrograde amnesia present?

Despite the fact that some of the patients were in the very earliest stages of DAT, all were significantly impaired on tests of anterograde memory. The pattern of impairment on remote memory was, however, more variable; the regression analysis indicated that there was a limited association between severity of remote memory impairment and severity of dementia. The striking lack of correlation between anterograde and retrograde tasks is in keeping with previous studies of patients with DAT [188] and the amnesic syndrome [188, 297]. Adopting a case-by-case approach, some patients with minimal DAT had clear-cut remote memory impairment, while some with more established DAT (as measured by anterograde and other cognitive tests) were relatively preserved on remote memory tasks. As previously mentioned, anterograde amnesia is thought to arise from pathology affecting the transentorhinal region, which disrupts hippocampal connections [42, 160]. It is less clear which anatomical structures are implicated in the development of a retrograde amnesia [101, 140, 173, 188, 208, 308], but the key structures appear to be the temporal neocortex (which is important for memory storage) and frontal systems perhaps acting via the diencephalon (which play a key role in remote memory retrieval). The fact that all my patients were impaired on anterograde tasks suggests that they all have perihippocampal pathology. The variability in retrograde memory implies that other anatomical structures are much more variably affected by the disease. I shall return to this issue when discussing autobiographical memory in Chapter 5.

What components of face and name processing are affected in DAT ?

My results broadly agree with those by Hodges *et al* [148] who found the main locus of pathology, in cognitive terms, to be at a semantic level. As in the former studies, I found all components of face processing to be impaired, i.e. face recognition, identification and naming. I have extended these findings to show that name recognition and identification are also defective in DAT.

The finding that recognition of faces is impaired in DAT suggests that face recognition units are damaged. I would argue, however, that the primary defect is in stored semantic knowledge: the DAT patients identified a significantly smaller proportion of the faces that they recognised than did the controls. In addition, the DAT patients named a significantly smaller proportion of the faces that they identified than did the controls; this suggests that post-semantic processing may be

impaired, and that the deficit in naming may not simply reflect impaired semantic knowledge. Alternatively, the naming deficit may be explained by partial semantic impairment. According to this explanation, patients with partially degraded semantic stores may be able to produce some specific information (e.g. "he's an American president"), but this is insufficient to activate the appropriate phonological representation (Ronald Reagan). To test this hypothesis, it would be necessary to probe more extensively for knowledge about named and unnamed faces. The assumption on year 1 testing that intact naming meant that identification was preserved may not be true. In order to assess this point, I reversed the order of testing on year 2, examining identification prior to naming. This allowed me to address the issue of naming without semantics, and will be discussed in Chapter 4.

Recognition and identification of famous names has not been previously explored in DAT patients. I found that DAT patients were impaired on both recognition and identification of famous names with respect to controls. This suggests that name recognition units, and person-specific semantics as accessed by names, are also damaged in DAT.

Contemporary models of face and name processing differ subtly. They range from serial processing models of face [47] and name processing [333] to interactive activation and competition IAC models [52, 54]. Both Valentine *et al*'s [333] development of the Bruce and Young model [47], and Burton and Bruce's interactive activation and competition IAC model [52, 54] assert that there is a unified semantic knowledge base of people, whether accessed by faces or names. Thus both models would predict that there would be a strong association between face and name identification. This was confirmed by the present data.

With regard to face and name recognition, Valentine *et al*'s serial model postulates separate face and name recognition units, and would predict that face and name recognition were dissociable. Burton and Bruce's IAC model suggests that recognition and identification share a common pool, and would predict a stronger association between face and name recognition than Valentine *et al*. The use of a forced-choice paradigm in my tests complicates interpretation, making it difficult to draw firm conclusions from my data. On the one hand, I found a stronger association between famous face and famous name recognition than might be predicted from the older serial processing models, but on the other hand I found instances of normal name recognition but impaired face recognition, and vice versa. Moreover, the IAC model is undergoing constant development [45], which will affect predictions regarding the association between face and name identification.

In conclusion, these findings show that all components of face and name processing are impaired early in the course of DAT but that the major damage falls on the semantic system underlying person identification. Converging evidence supports

the hypothesis that faces and names do indeed access a common pool of knowledge. It is less clear whether face and name recognition processes share common determinants.

Is knowledge of famous people related to general semantic memory ?

Turning to the question of the relationship between famous person and general semantic knowledge, I found that the correlation between them was poor. Knowledge of famous people accessed by famous names did correlate with some semantic tasks, while there was no such correlation between famous face and semantic tests.

My data suggest that general and person-based knowledge are dissociable, and would be in keeping with anatomical evidence. As discussed above, the neural basis for semantic memory is not well established but current evidence points to the temporal neocortex as the key region [82, 84, 144, 256]. The bases for separate domains of knowledge within the semantic system is, however, much less certain; patients with apparently localised left temporal pathology can show deficits in both verbal and visual knowledge of manmade objects and living things [144, 145, 256]. The limited evidence currently available suggests that the right temporal lobe might show equivalent specialisation for person-based semantic knowledge [103], although it may be represented in both temporal lobes [270]. Given that person-specific and general semantic memory appear to be subserved by different anatomical structures, it is not surprising that there may be dissociations in performance between these two cognitive modules.

Summary

I assessed remote memory in 33 patients with dementia of Alzheimer's type (DAT) with Mini-Mental State Examination scores between 17 and 30 and 30 matched controls using a Famous Faces Test and Famous Names Test designed to assess face recognition, identification and naming, and name recognition and identification, respectively, together with a range of anterograde episodic and semantic memory tests.

Patients with DAT were impaired on all components of the remote memory tests, i.e. famous face recognition, identification and naming, and famous name recognition and identification. There was also evidence of a modest temporal gradient, with relatively greater impairment of more recent memory, which may be artefactual resulting from the very insidious onset of their anterograde amnesia.

In contrast to the uniform impairment of anterograde memory, there was considerable heterogeneity in performance on remote memory. Although the DAT patient group's performance on remote memory measures was impaired with respect to controls, some patients had significant impairment on all measures, whereas others had intact remote memory. Overall, there was only a weak correlation between

dementia severity and remote memory, and no correlation between performance on the Faces and Names tests and measures of anterograde memory.

At a cognitive level, the deficit in face and name processing in DAT involved recognition, identification and naming. This would suggest that so called "face and name recognition units", semantic knowledge of famous persons and post-semantic processing are all affected by the disease. There was also supporting evidence for the concept that recognition of famous faces and names both draw on common sources. Similar results were found for face and name identification. This suggests that face and name recognition units are closely linked, and that identification of a face or name accesses the same central pool of semantic knowledge regarding the famous person.

Performance on famous names tests correlated, to a limited degree, with that on general semantic tests, suggesting that knowledge of famous people, at least as accessed by names, is associated with general semantic memory. By contrast, no correlation was found between performance on the famous faces and on other general semantic tasks.

Chapter Four

Knowing about people and naming them: Can Alzheimer's patients do one without the other?

Introduction

As discussed in the previous chapter, it is now well established that patients with dementia of Alzheimer type (DAT) show substantial impairment on tests involving the naming of famous faces [25, 148, 360]. Indeed, my own study has confirmed that even early in the course of the disease, DAT patients show substantial deficits which are due to loss of knowledge regarding the famous persons. The objectives of this chapter are to address the issue of whether patients with DAT can ever name the faces of people whom they do not know. In other words, is there evidence for naming without semantics ? A secondary objective was to see whether the evidence from face identification and naming in DAT favoured classic information processing models of face identification or more recently developed interactive computational models.

The model of Bruce and Young [47] has already been discussed in Chapter 3 and will be discussed briefly here (see Figure 4.1). In this framework, the recognition, identification and naming of known faces involve a sequence of discrete cognitive processes. First, structural encoding of the perceptual features provides a visual description of the seen face. Recognition of the face as familiar proceeds by comparing this description to the store of known familiar faces (or face recognition units [FRUs]). The Bruce and Young model maintains that judgement of face familiarity is based on activation of these domain-specific recognition units. The next stage of processing involves activation of a "person identity node" (or PIN), which represents semantic information about the person[1]. It can be seen from Figure 4.1 that PINs may be activated by other means. The person's voice, or the heard or seen name (via name input codes) can stimulate the PINs, allowing access to semantic knowledge. Once semantic information is accessed, naming requires the additional activation of phonological name output codes and subsequent articulatory processing.

It has been established that failure to name a picture of a famous person may, therefore, reflect an impairment at any level of this sequence [363]. In classic prosopagnosia, the FRUs are damaged, yet patients may access semantic information regarding people if PINs are activated by means of heard voice or name etc. Preserved familiarity but impaired access to semantic information has also been described [86]. Loss of semantic knowledge for people has also been demonstrated [101, 103, 128]. From the point of view of the present study, it should be emphasised that, in the Bruce and Young model, the name for a face can only be retrieved via semantic knowledge about the person to be named.

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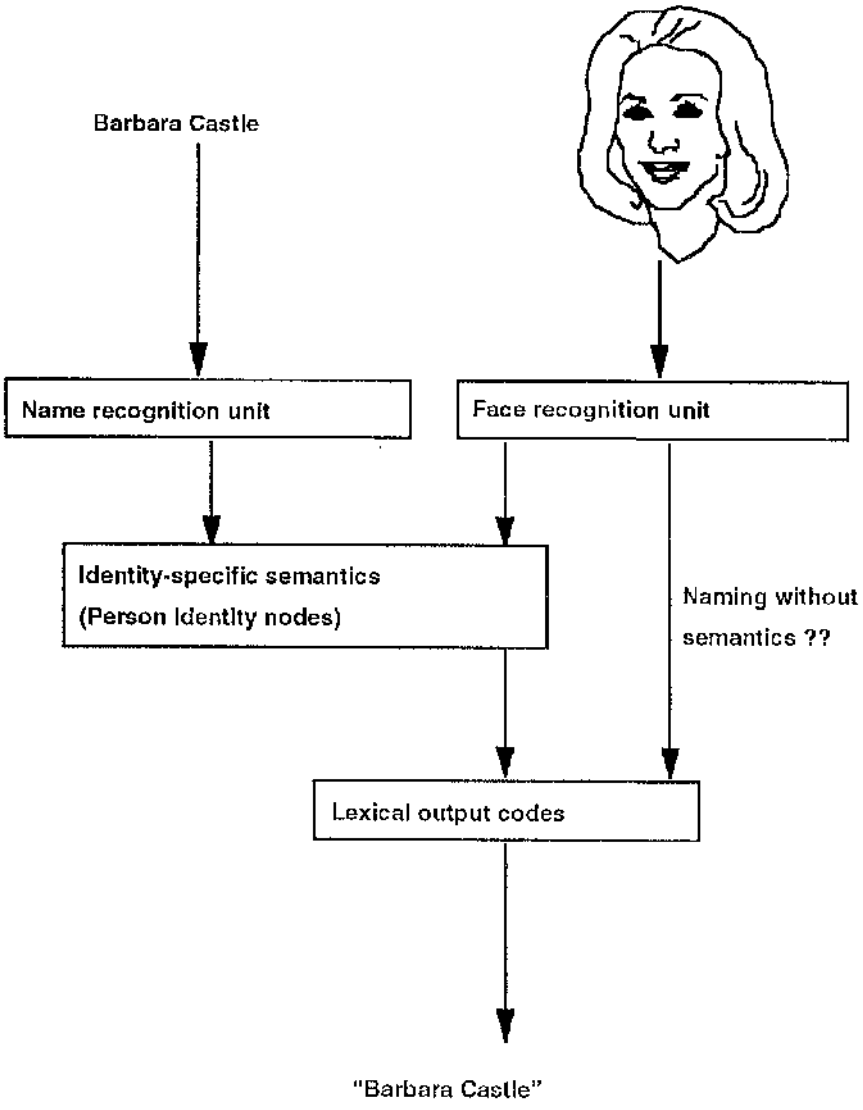
[1] The issue of whether PINs actually contain person-specific semantic information or alternatively act as the gateway of access to such information was left deliberately ambiguous by Bruce and Young [47]. I have adopted the former position here for simplicity.

Previous studies have noted that the production of names from faces is slower and less accurate than the production of other semantic information. This is based on the assumption that the phonological elements of a person's name are activated only after specific semantic information is accessed, and that names may not be produced in the absence of such information. In support of this, Flude *et al* [108] reported a patient who demonstrated preserved access to person-specific information, but impaired name retrieval. It is not, however, necessary to be able to access all semantic information in order to produce a name [365, 366].

Figure 4.1. A model of face processing with the putative pathway for naming without semantics



A variant of the Bruce and Young model has been implemented as an interactive activation and competition (IAC) model [52, 54]. To achieve a successful implementation able to account for effects established experimentally, Burton *et al* had to make some modification to the Bruce and Young framework. Burton *et al* claimed that PINs form modality-independent gateways to semantic information about identity, rather than themselves containing semantic information. Their model differs from that of Bruce and Young in that familiarity decisions occur at PIN level, rather than solely on the basis of activation of FRUs. Thus, PINs serve as common access points to identity-specific semantic information from domain-specific analysers of faces, names, voices, etc.

In their IAC model, Burton and Bruce [52] propose that a person's name is coded along with other semantic information at the level of the semantic information unit (SIU): just as there are units coding occupation (e.g. politician) and nationality (e.g. British), so there are also units that code, for example, "Name is Margaret Thatcher"(p 462).[2]

According to the IAC model, if a FRU is activated this passes activation to the appropriate PIN. In turn, activation is passed to all the SIUs connected with that person (politician, British etc). Because of the bidirectionality of the links, it is always the case that SIUs that are unique rise more slowly and to a lower asymptotic activation than SIUs shared by other people. Viewing the face of Margaret Thatcher will activate the politician SIU, which in turn passes a small amount of activation back to the PIN pool to other politician PINs. This activation then feeds forward again into the SIUs. It follows from this that SIUs that are unique will tend to receive less activation than shared SIUs. Thus, it is argued that it is the unique status of the SIU coding "Margaret Thatcher" which accounts for everyday deficits in name retrieval. However, certain semantic information may be of similar uniqueness to the proper name. With the example of Margaret Thatcher, "Born in Grantham" is likely to be of comparable uniqueness to her proper name, in that most people will only know of one famous person who was born in Grantham.

Although the above two models both predict that naming is impossible in the absence of other identifying semantic information, there are subtle differences between them. Burton *et al* [54] place familiarity at the level of the PINs, rather than the FRUs as suggested by Bruce and Young. Burton *et al* predict that, if face and name are familiar only, then the PIN should allow the subject to state whether the face and

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[2] Since naming a face obviously requires the activation and retrieval of the appropriate phonological representations, the nature of the "name information" represented at the semantic information unit level is unclear. I assume that this is equivalent to the abstract representations envisaged at the semantic lexicon [60] or lemma [198] level of processing postulated in models of object naming.

name are of the same person. The Bruce and Young model, by contrast, would not predict that familiarity for faces and names would correspond in this manner. The former view has been borne out experimentally [86]. Support for the IAC model also comes from studies of semantic and repetition priming [54] and covert recognition [55].

Another difference between the models relates to the status of semantic information in the context of impaired naming. The Bruce and Young model, arguing for the strict separability of semantic information and names stores, would predict that patients may show impaired name retrieval but totally preserved semantic information. The IAC model, however, suggests that whenever names are lost, it would be inevitable that semantic information, of similar uniqueness to names, should also be lost (i.e. that information which is unique to the known individual). Using the previous example, if "Margaret Thatcher" is lost, then information such as "Born in Grantham" should also be lost.

Turning briefly to studies of general semantic memory, it is generally accepted that object naming is only possible if semantic knowledge of the object is present, e.g. naming an object as a banana is only possible if knowledge about bananas is retained [100, 217]. However, a number of researchers have hypothesised that there may be an alternative route to visual naming, i.e. directly from the pre-semantic level of stored structural representation to the phonological output lexicon [135, 192, 264]. It has been proposed that a selective deficit of semantic knowledge sparing this path could lead to preserved object naming in the absence of identifying semantic knowledge. In support of this, it has been claimed that patients with DAT can name objects while having lost semantic knowledge of the same items [193, 298], although this remains controversial.

Extending the analogy of "naming without semantics" to person-specific knowledge, one can ask whether a patient with severely disrupted semantic knowledge about a previously familiar person would ever be able to name that person's face (see Figure 4.1). To date, there have been no unequivocal demonstrations of retrieval of a name in the absence of some personal information, whether by naturalistic 'diary' [366] or by large-scale laboratory study [134].

To see if there is any evidence for a non-semantic naming route for faces, it would be appropriate to use patients with a disease process where semantic memory was impaired. It is known that semantic memory is impaired in DAT, making this an ideal model to address this issue [66, 143, 149, 213]. My primary aim was to see if there was any evidence for a syndrome analogous to naming without semantics with respect to famous face naming, i.e. were there any instances where the subject was

unable to give any identifying information regarding the famous face, yet could produce the name? These data should provide a definitive answer to this question.

A secondary aim was to see whether these data could be used to argue for or against the Bruce and Young serial face processing model or the Burton *et al* IAC model. The former model would predict that impaired naming might be present even with intact semantic knowledge as evidenced by the production of unique identifying information. The IAC model, by contrast, would predict that deficits in name retrieval would inevitably be accompanied by loss of semantic information of a similar uniqueness to the name of the famous face.

Methods

Subject groups

Two groups consisting of a total of 54 subjects participated in the study: 24 patients with DAT (15 females and 9 males) and 30 neurologically intact normal control subjects (15 females and 15 males). Written informed consent was obtained from all subjects or the caregivers, where appropriate.

The DAT patient group comprised those tested at year 2. I could not use year 1 data as I had made the assumption that preserved naming automatically indicated preserved identification. On year 2, I tested recognition and identification followed by naming in all circumstances.

Tests

The Famous Faces Test employed here is described in Chapter 2.

Statistical analysis

Overall scores were analysed using unpaired comparisons and Analysis of Variance (ANOVA) with repeated measures. Post hoc pairwise comparisons were made using Student-Newman-Keuls test. Furthermore, for each patient, performance for each famous face was assessed: as I was particularly interested in whether naming without semantics could occur, I studied performance on identification and naming for each famous face by each subject. This item-by-item approach led to 50 entries for each of the 24 patients. I therefore had 1200 patient-responses, which were entered into a contingency table.

Results

Overall scores for recognition, identification and naming of famous faces for DAT patients and controls are shown in Figure 4.2. Results for recognition, identification and naming were analysed by means of ANOVA with repeated measures. There was a significant group effect ($F[df\ 1,52]=40.4$, $p<0.0001$), a condition (recognition vs

identification vs naming) effect (F[df 2,104]=322, p<0.0001), and a significant group by condition interaction (F[df 2,104]=74.8, p<0.0001). Post hoc analysis indicated that this was due to DAT patients being selectively impaired for naming with respect to identification (P<0.05), and for identification with respect to recognition (P<0.05). These findings are virtually identical to those presented in Chapter 3.

Figure 4.2. Performance on famous face recognition, identification and naming by DAT patients and controls, with standard error bars

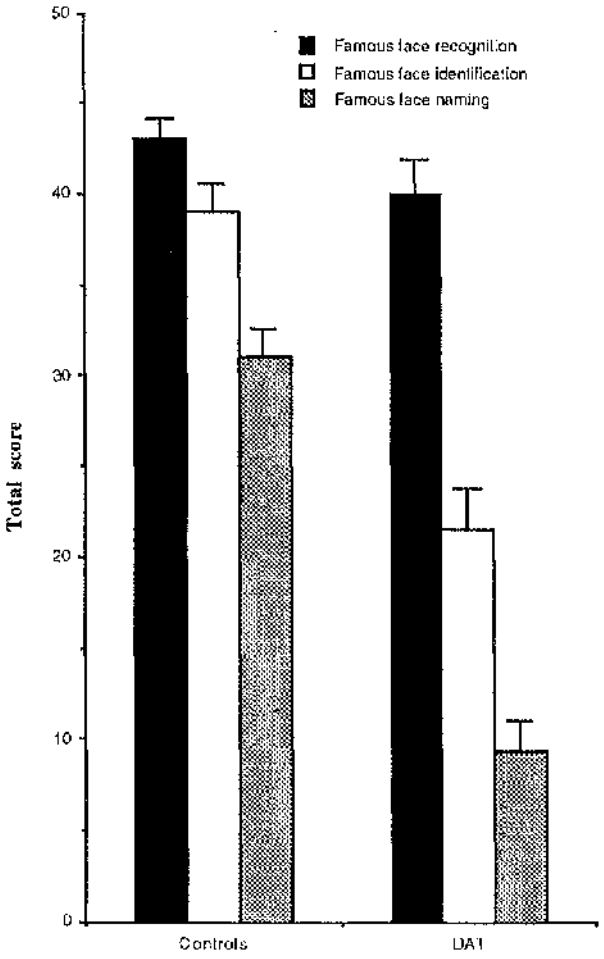


Table 4.1 illustrates performance on famous face identification and naming by the 24 DAT patients for the 50 famous faces. It can be seen that performance on identification tended to be in accordance with performance on naming. On 564 occasions, subjects could neither identify nor name a famous face, while on 200 occasions they could do both. On 206 occasions, the subject could produce sufficient identifying information to uniquely identify the face, but be unable to produce the name.

I realise that I am not totally justified in using Chi Square analysis, as this requires each observation to be independent; as I have data on 50 famous faces by 24 patients, then the data are related either by face or by subject. Bearing in mind this reservation, a contingency analysis indicated that there was a strikingly significant association between identification and naming (Chi Square = 473.9, $p<0.0001$).

Table 4.1. Results of famous face identification and naming for each of 50 famous faces by 24 DAT patients. Sign indicates whether actual number is more (+) or less (-) than would be expected by chance, (with Cell Chi Squares in brackets)

		Naming		
		0	1	Total
Identification	0	564 (+)(21.9)	2 (-)(98.9)	566
	0.5	212 (+)(3.5)	16 (-)(15.6)	228
	1	206 (-)(48.0)	200 (+)(216.1)	406
	Total	982	218	

My main aim was to see whether it was possible to have no identifying knowledge about a person, and yet be able to produce the name. It can be seen that this occurred on only two instances. These two responses were analysed, therefore, in greater detail. In one instance, the subject correctly recognised the photograph of Louis Mountbatten as being famous. On being asked to identify the face, the subject said, "I think he was in the House of Commons", but she could not produce any more unique identifying information. Naming the photograph as Louis Mountbatten was subsequently achieved. Although the identifying remarks were scored as zero, it may be possible that the subject's premorbid identifying information was incorrect. Mountbatten was an admiral, Viceroy of India and related to the royal family. He became a Lord, which allowed him to sit in the House of Lords. Thus the subject may have falsely previously held the belief that Mountbatten was in the House of Commons.

In the second instance, a different subject recognised the photograph of Diana Dors as being famous, and stated, "She was a comedian, I expect", but could not produce any more unique identifying information. He could subsequently produce the name "Diana Dors". Diana Dors was an actress and although some of her starring roles involved comedy, she was primarily a sex symbol. Thus, although the subject was technically incorrect, he could be forgiven for thinking she was a comedian.

On 16 occasions, the subject could produce the name but was only able to give broad identifying information. An example of this would be "He's a politician, can't remember which party or when, I think he got into trouble", earning 0.5 marks, followed by correct production of the name "John Profumo".

Further examples of incomplete identification but correct naming follow.

Rab Butler: politician, Liberal-Democrat I think
Rab Butler: politician, Labour I think
Ronald Reagan: a politician
Harold MacMillan: Labour Prime Minister five years ago
Ayatollah Khomeini: I think he's from the Far East, a leader
Michael Heseltine: politician, not sure which party
Michael Heseltine: British politician
Michael Heseltine: politician (On cueing, subject had no recollection of Heseltine's recent health problems)
Esther Rantzen: does things for people on TV
Peter Sellers: in films
Ayatollah Khomeini: boss of Egypt
Joseph Stalin: dictator abroad
Neil Kinnock: politician, not sure which party

In conclusion, therefore, there were essentially no cases where a subject was able to name a famous face having failed to produce any correct identifying information regarding why the person was famous. There were 16 instances in which subjects produced incomplete responses but were able to name correctly the person represented. Of course, I cannot know whether the subjects every knew more about the person represented. It is possible that these responses reflect intact naming in the presence of partially degraded semantic information. I can, however, conclude that naming is never possible in the absence of some correct knowledge about the target person.

The secondary aim was to see if the data could be used to assess the relative merits of the Bruce and Young and IAC models. While the former model can

accommodate impaired name retrieval with intact semantic information, the latter cannot so readily deal with this pattern. There were 206 instances in which the subjects could produce unique identifying information "He's a Tory MP in the Cabinet in the 1960s who was forced to resign because he had an affair with a prostitute who was passing information on to the Russians" yet be unable to produce the name "John Profumo". Other examples include "She's a television presenter who did *That's life* and founded ChildLine" but could not access "Esther Rantzen", and "He's a cricketer who's not popular with the authorities who did a sponsored walk from John O'Groats to Lands End to raise money for leukaemia" but could not produce "Ian Botham". These descriptions appear to contain information specific to the target personality which in the IAC model have the same status as their names and support, therefore, the Bruce and Young serial processing model rather than the IAC model. In summary, DAT patients may be unable to produce the appropriate name yet have access to highly unique semantic information about the target person.

Discussion

To investigate the possibility of a syndrome equivalent to naming without semantics for person-specific semantic knowledge, I studied identification and naming of 50 famous faces in 24 DAT patients. The most striking finding was that out of 1200 (24 x 50) opportunities, there were no clear instances, and only 2 dubious instances, of successful naming in the absence of any semantic identifying information. Although I generalise from models of person-specific to general semantic memory with caution, my findings have some implications for the architecture of semantic knowledge. I have found no support for the contentious theory that there may be a direct route for naming which bypasses semantics, by going directly from the pre-semantic stage of object/face processing to the speech lexicon, as is suggested by the proponents of naming without semantics [135, 192, 193, 264, 298].

Shuren *et al* [298] suggested that naming without semantics may occur in the very earliest stages of DAT only. It should be noted that my patients represented a spectrum of severities from very mild to more established disease as demonstrated by the range of their MMSE scores (17-30), yet none exhibited non-semantic naming. Clearly one cannot say that this never occurs, but in the context of DAT I have found no supportive evidence and I have no reason to believe that different pathologies would affect cognition differentially.

My study was primarily concerned with the issue of whether naming could occur in the absence of identifying information, and was not designed to address the relative strengths of the Bruce and Young and IAC models. As highlighted in the Introduction, however, the relationship between identification and naming does bear

on the relative merits of these models. Many of my patients were able to produce very detailed identifying information in the context of an inability to name. This pattern would be more in keeping with the model of Bruce and Young, which posits name stores separate from semantic information, rather than the IAC model, which predicts loss of name retrieval to be accompanied by loss of other semantic information of equivalent uniqueness. It is obviously difficult to identify aspects of semantic information that are equivalent in uniqueness to the person's name. Although being a Tory Minister brought down by a sex scandal involving leaking of government secrets to a Russian official might be thought to be as unique as the name "John Profumo", such studies comparing semantics and name retrieval are necessarily subjective. Even the information given above is not necessarily of similar uniqueness to the name. The several pieces of semantic information are not unique; it is the intersection of these items that is unique to John Profumo. I feel, therefore, that my findings offer only limited support for the classic serial processing rather than the IAC model.

In conclusion, my study has been inconclusive in supporting or refuting one or other face processing model. However, I feel I have definitively rebutted the concept of naming from faces without semantics.

Summary

I studied recognition, identification (the ability to provide accurate information) and naming of 50 famous faces by 24 patients with mild to moderate dementia of Alzheimer type (DAT) and 30 age-matched controls. The DAT group was impaired in all three conditions. An analysis of the concordance between identification and naming by each patient for each stimulus item established that naming a famous face was possible only with semantic knowledge sufficient to identify the person. My data support the hypothesis that naming is not possible unless semantic identifying information associated with the target is available. Naming without knowing, therefore, does not occur, at least in patients with DAT. By contrast there were 206 instances (17% of the total responses) in which the patients were able to provide accurate identifying information yet were unable to name the person represented. This pattern is more easily accommodated by the Bruce and Young processing model of face identification which posits separate stores for semantic information and names, rather than the interactive activation model of Burton *et al.*

Chapter Five

Executive function and autobiographical memory in early dementia of Alzheimer type

Introduction

Remote memory has been investigated relatively little in DAT [140]. Although early studies focused on memory for public events and famous faces [280, 360], more recently there has been interest in autobiographical memory. Autobiographical memory does not fit neatly into the episodic-semantic dichotomy [329]: in a study by Dall'Ora *et al* [78] in DAT patients, no correlation was found between autobiographical, and anterograde episodic or semantic memory.

It has been proposed that frontal lobe-based "executive" functions are vital for the retrieval of autobiographical memories, but this hypothesis remains controversial [90, 91, 185, 238]. The primary aim of this chapter is to investigate the relationship between executive function and autobiographical memory in my cohort of patients with minimal to mild DAT to see if there is support for the executive-autobiographical hypothesis. A secondary objective was to see at what stage of the disease executive function and autobiographical memory become impaired.

Amongst the many cognitive abilities ascribed to the frontal lobes, there is converging evidence linking the central executive component of working memory to the prefrontal cortex. The central executive plays a critical role in controlling two putative slave systems responsible for the immediate recall of verbal and visual information, namely the phonological loop and the visuo-spatial sketchpad [13, 18]. The central executive is assumed to be particularly important for manipulating information in dual-performance and other tasks with a major divided attentional component. It is also the aspect of working memory which has been implicated in autobiographical memory.

Patients with DAT exhibit deficits in working memory and are known to be impaired on tests which stress the central executive aspects of working memory [14, 19, 185]. It is uncertain, however, how early in the course of DAT such deficits occur. In addition, the relationship of working memory to autobiographical memory in patients with DAT has been explored only infrequently [185].

Before addressing the potential role of working memory in autobiographical memory, a few theoretical points will be considered. The term autobiographical memory has been applied to the component of remote memory responsible for personally-relevant past memories, but autobiographical memory has itself been further subdivided [189] into personal semantic memory (e.g. name of primary school), and autobiographical incident memory (e.g. memory of an event from schooldays). Clearly the broad term autobiographical memory covers a range of types of information which may have a separate cognitive and neural underpinning. Initially, all personal memories are likely to be episodic in nature, but it has been suggested that some episodic (time-specific) traces lose their contextual dependence, when

spontaneously recollected many times [64, 267], and acquire the schematic features and generic organisation common to semantic knowledge [289]. Retrieval of personal semantic memory may be similar to evoking general semantic memory, while accessing autobiographical incident memory may involve a more active and reconstructive retrieval and recollection process [11].

Patterns of remote memory impairment have led some theorists to propose alternative models of remote memory processing, most notably perhaps the thematic retrieval framework model. According to this model, the process of recollection and remembering is conceived of as a dynamic cognitive operation involving problem solving, cross-checking, verification and inference [245]. Retrieval is mediated via a hierarchical program; at the lowest level are the elements of autobiographical records which may be fragmentary and cognitively unstructured; at the highest level of the program are retrieval "frameworks", organised thematically, in terms of major life events or lifetime periods [70]. By accessing the retrieval framework appropriate to one or other life epoch, a major organisational structure is provided that can guide retrieval and reconstruction of more specific autobiographical episodes [70, 268]. The frontal lobes and closely related diencephalic structures are regarded as playing a critical role in autobiographical memory retrieval, reconstruction and cross-verification [141].

Damasio [81] has proposed a related model of how autobiographical memories are encoded, stored and recalled. It is claimed that when we experience an event, it is stored in different regions of the brain as a space- and time-locked multimodal memory. For each modality, aspects of the event are stored in the appropriate association cortex. Concurrently, an abstract, amodal "binding code" specifies the location of the various unimodal memory stores or "templates" associated with that event. The different aspects of the event are synchronised in "convergence" regions of the brain which have rich connections with all the association cortices. It is suggested that these "convergence" regions include the frontal cortex.

Thus both the thematic frameworks and the time-locked multiregional models propose a prominent role for frontal executive function in the retrieval, construction and verification of autobiographical memories. In support of this hypothesis, Tulving has noted increased frontal blood flow when subjects are asked to retrieve autobiographical memories [330]. The neuropsychological evidence that frontal lobe damage produces deficits in autobiographical memory is, at present, rather limited and contradictory. In Della Sala *et al*'s [90] study of patients with frontal damage, poor autobiographical retrieval correlated significantly with executive test performances and with the CT-verified bilaterality of the frontal damage. However, other studies have failed to corroborate these findings. Dall'Ora *et al* [78] found no clear link between

autobiographical memory and frontal atrophy or dysfunction in amnesics and DAT patients. Kopelman [188] found no correlation between frontal atrophy and autobiographical memory in patients with Korsakoff's syndrome, although admittedly atrophy is not synonymous with executive dysfunction. In another study, Kopelman found only a weak correlation between frontal function and retrograde amnesia [185]. Moreover, extensive retrograde amnesia for autobiographical memory has been documented in the absence of frontal dysfunction [24].

Although there are considerable theoretical grounds for believing that the frontal lobes are implicated in retrieval of autobiographical memory, other anatomical structures may also be involved in this retrieval process. It has been claimed that the non-dominant temporal lobe may be also necessary for reconstructing autobiographical memory by using visual imagery [247, 250]. In addition, it is quite feasible that certain aspects of executive function are important for either the personal semantic or incident components of autobiographical memory. This possibility has not been fully explored.

Loss of autobiographical memory could also arise from destruction of the individual memory traces rather than disruption of the retrieval and verification processes discussed above. Since autobiographical memories are usually complex and multi-modal comprising visual, verbal and other sensory components, the individual elements are likely to be stored in predominantly posterior association cortices. Since we know that semantic memory is impaired from early in the course of DAT [136, 143, 148, 149], it follows that loss of the individual elements of autobiographical knowledge may also occur. By administering two tests of autobiographical memory with very different retrieval demands, I hope to address the issue of whether any impairment of autobiographical memory is due to a high level retrieval deficit or loss of memory stores.

Turning to studies of autobiographical memory in DAT, Sagar *et al* [280], using a modified Crovitz test in which autobiographical memories are prompted by cue words [73], found poor recall of specific life-events with evidence of a temporal gradient in that DAT patients tended to produce memories from the more distant past than controls. However, this apparent temporal gradient may be due to subjects' bias to report memories from particular time-periods rather than their capacity to do so [190]. Using the Autobiographical Memory Interview (AMI), which probes for both personal semantic and incident memories from each time period, Kopelman [188] found that autobiographical memory in DAT was impaired, with evidence of a gentle temporal gradient, but that there was no dissociation between the personal semantic and autobiographical incident components; it has been suggested, however, that this study may have failed to detect a dissociation on account of a ceiling effect [96].

Dall'Ora *et al* [78] used a schedule very similar to the AMI and also found impaired autobiographical memory in DAT, again with no temporal gradient; their test however considers only incident memory. It should be noted that all of these studies have involved patients with established disease and all but one [78] have considered group data only. It is quite likely that considerable heterogeneity exists in patients with DAT related to the progression and distribution of the neuropathological lesions.

It is clear from this review that considerable uncertainty exists concerning the status of autobiographical memory in general and, more particularly, the nature of its involvement in DAT. I set out to resolve the following questions i) Is autobiographical memory consistently impaired early in the course of DAT ? ii) Is there evidence of a temporal gradient ? iii) Is the central executive component of working memory defective in early DAT ? iv) What is the relationship between frontal executive and autobiographical memory in DAT ? and v) Is there evidence from this study of separate subcomponents within autobiographical memory and executive function ?

Methods

Subjects

This cross-sectional study utilise the data collected at year 1 on 33 DAT patients and 30 controls. Further details are given in Chapter 2.

Tests

The tests of executive function and autobiographical memory are described in Chapter 2.

Results

Effects of disease severity on executive function

1. Della Sala *et al*'s dual performance task

As can be seen in Table 5.1, comparison of the controls and DAT groups' mean digit span showed a significant group effect ($F(2,60)=5.25$, $p<0.01$). Post hoc pairwise comparisons using the Student-Newman-Keuls method revealed that controls performed significantly better than mild DAT patients ($p<0.005$), but that there was no difference between controls and minimal DAT patients, or minimal and mild patients. Interestingly, there was no significant difference between the groups in the proportion of digit span sequences correct over two minutes in the single task component ($F(2,60)=1.52$, $p>0.05$). Analysis of the number of boxes filled, as part of the single task, showed a significant group effect ($F(2,60)=5.30$, $p<0.01$) with controls ($p<0.005$) and minimal patients ($p<0.05$) performing significantly better than mild patients (i.e. controls = minimal > mild).

In analysing the results in the dual-task condition I considered a number of measures. Firstly, comparison of the proportion of digit span sequences correct in the dual task component revealed no significant group effect ($F(2,60)=1.73$ $p>0.05$). By contrast, the number of boxes filled in the dual task differed significantly ($F(2,60)=10.1$, $p<0.0005$) with controls performing better than either minimal ($p<0.05$) or mild group ($p<0.0001$) (i.e. controls > minimal = mild).

Secondly, the proportion of digit span sequences correct on the single and dual task components were compared using a 2 (conditions) X 3 (groups) ANOVA with repeated measures. There was no group effect ($F(2,60)=1.78$, $p>0.05$) and although there was a highly significant effect of conditions (single vs. dual task) ($F(1,60)=32.8$, $p<0.0001$), there was no significant interaction between the nature of the task and subject group ($F(2,60)=0.98$, $p>0.05$). The number of boxes filled on the dual task as a percentage of boxes filled on the single task showed a group effect ($F(2,60)=8.35$, $p<0.001$), controls performing better than both minimal ($p<0.005$) and mild ($p<0.001$) patient groups.

Thirdly, performance was expressed as a dual task decrement. This score represents the additional time taken to fill each box in the dual task condition with appropriate adjustment for differential levels of performance on the dual task (i.e. a score of 1.4 for normal controls means that they took an extra 1.4 seconds to complete each box in the dual task). The negative of the dual task decrement was expressed as a measure of dual task performance. One-way ANOVA of dual task performance showed a significant group effect ($F(2,60)=6.5$, $p<0.005$) (see Figure 5.1), and post hoc comparisons revealed that controls ($p<0.001$) and minimal patients ($p<0.05$) performed better than mild patients (i.e. control = minimal > mild).

Table 5.1. Performance of the controls and DAT patients on Dells Sala et al's dual performance task showing mean scores (with standard deviation)

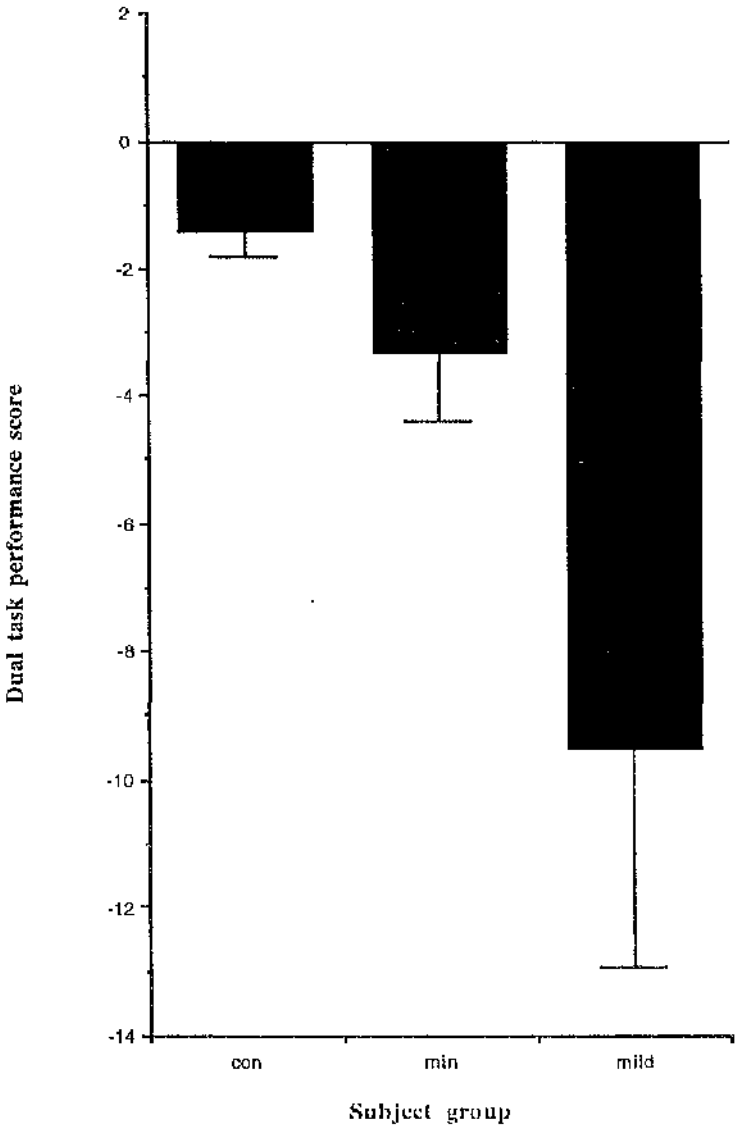
Della Sala *et al*'s dual performance task		controls	minimal DAT	mild DAT (SD)	p-values
Single task	digit span	6.0 (0.7)	5.6 (0.9)	5.2 (1.0)	<0.01§
	% digit spans correct	76 (20)	77 (25)	65 (28)	NS
	boxes filled	120 (38)	112 (39)	82 (40)	<0.01§¥
Dual task	% digit spans correct	57 (24)	67 (25)	51 (25)	NS
	boxes filled	107 (34)	77 (46)	52 (47)	<0.0005†§
Combined dual/single	digit span sequences	0.76 (0.29)	0.93 (0.36)	0.82 (0.30)	NS
	boxes filled	0.9 (0.27)	0.67 (0.29)	0.61 (0.33)	<0.001†§
	combined performance	-1.4 (2.2)	-3.3 (4.5)	-9.5 (13.5)	<0.005§¥

† significant difference between controls and minimal DAT subgroup

§ significant difference between controls and mild DAT subgroup

¥ significant difference between minimal and mild DAT subgroups

Figure 5.1. Dual task performance for Della Sala et al's dual task - digit span with simultaneous box cancellation - for controls and minimal and mild DAT patients, with standard errors



2. Dual task performance from TEA

A comparison of the groups' performance on the TEA is shown in Table 5.2. In the single task, the time taken differed significantly between the groups ($F(2,60)=9.58$, $p<0.0005$) with controls ($p<0.0001$) and minimal patients ($p<0.005$) performing better than mild patients (controls = minimal > mild). The number of symbols counted also differed significantly ($F(2,60)=3.38$, $p<0.05$), but only between controls and mild DAT patients ($p<0.05$). The time taken per correct symbol differed significantly between the groups ($F(2,60)=6.87$, $p<0.005$). Post hoc pairwise comparisons showed that both controls ($p<0.0005$) and minimal DAT patients ($p<0.05$) were superior to mild DAT patients (i.e. controls = minimal > mild).

In the dual task, analysis of the time taken showed a group effect ($F(2,60)=14.0$, $p<0.0001$) with post hoc pairwise comparisons differentiating all three groups (i.e. controls > minimal > mild, controls vs. minimal, $p<0.05$, controls vs. mild, $p<0.0001$, minimal vs. mild $p<0.01$). The number of symbols counted also showed a group effect ($F(2,60)=10.3$, $p<0.0001$) with mild DAT patients performing worse than controls ($p<0.0001$) or minimal patients ($p<0.005$) (i.e. controls = minimal > mild). The time taken per correct symbol differed significantly between the groups ($F(2,60)=7.92$, $p<0.001$). Post hoc pairwise comparisons showed that both controls ($p<0.0005$) and minimal DAT patients ($p<0.05$) were significantly superior to mild DAT patients (i.e. controls = minimal > mild).

A three (groups) X two (conditions) ANOVA with repeated measures was used to analyse the time taken between single task and the dual task symbol cancellation. There were significant main effects of group ($F(2,60)=13.2$, $p<0.0001$) and condition ($F(1,60)=9.59$, $p<0.005$) as well as a significant interaction between subject group and time taken ($F(2,60)=4.16$, $p<0.05$). Post hoc pairwise comparisons showed that both controls ($p<0.0001$) and minimal patients ($p<0.005$) performed better than mild patients (i.e. controls = minimal > mild).

A similar analysis of the symbols marked for single and dual task showed a group ($F(2,60)=7.75$, $p<0.001$) and condition effect ($F(1,60)=7.88$, $p<0.01$) but no interaction ($F(2,60)=0.33$, $p>0.05$).

Performance on the task was also expressed as a dual task decrement. One-way ANOVA showed a significant group effect ($F(2,60)=6.0$, $p<0.005$) (see Figure 5.2) and post hoc comparisons again revealed that both controls ($p<0.005$) and minimal DAT patients ($p<0.01$) performed significantly better than mild DAT patients, but that there was no difference between controls and minimal DAT patients (i.e. control = minimal > mild).

Thus, only the more impaired patient group showed a significant impairment in the dual task condition. It should be noted that this formula assumes that subjects

make no errors on tone counting on the single task. However, this assumption, if anything would lead to an overestimation of dual task impairment. Thus my finding of preserved executive function in minimal DAT is, if anything, strengthened.

Table 5.2. Performance of the controls and DAT patients on the dual performance task component of the Test of Everyday Attention showing mean scores (with standard deviation)

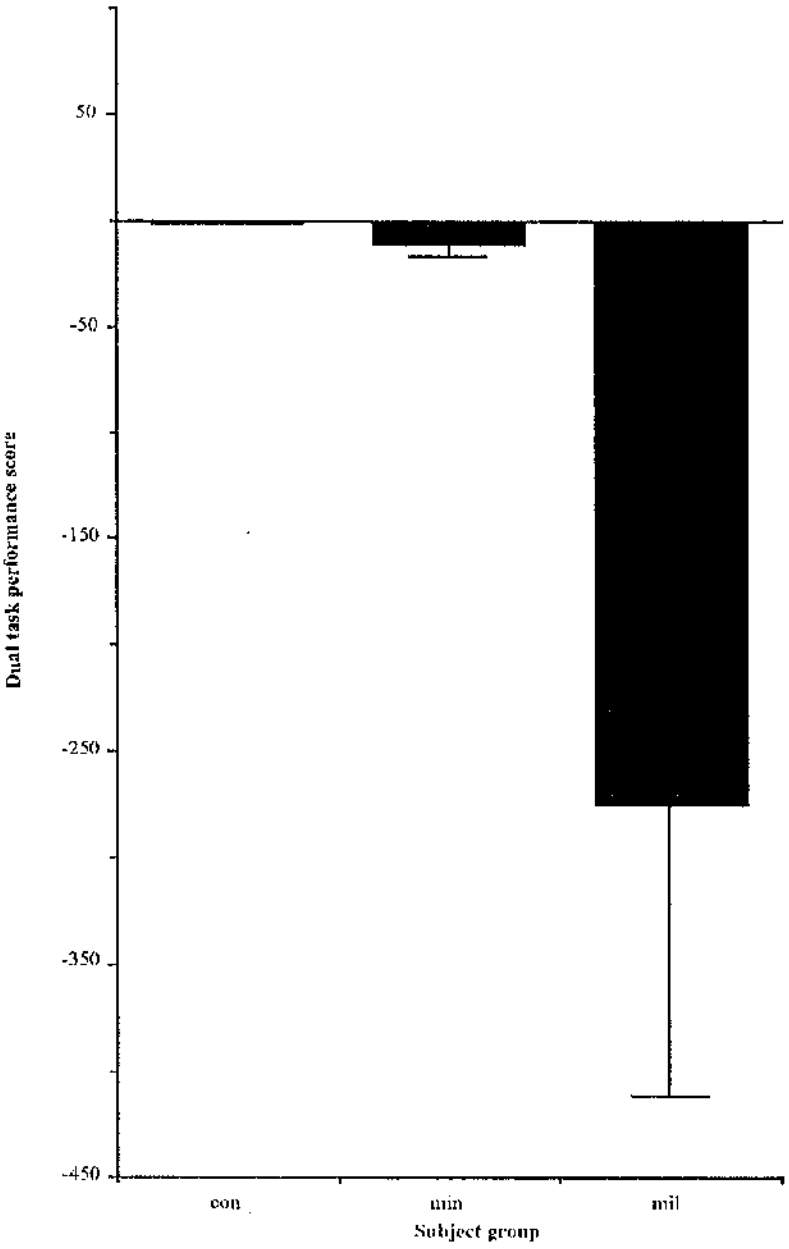
		controls	minimal DAT	mild DAT (SD)	p-values
TEA test					
Single task	time	91.2 (23.5)	106 (58)	170 (96.7)	<0.0005§¥
	symbols	19.5 (8.2)	17.2 (3.5)	14.3 (5.1)	<0.05§
	time/symbol	5.1 (1.6)	7.8 (10.6)	15.2 (13.9)	<0.005§¥
Dual task	time	91 (25)	137 (84)	203 (101)	<.0001†§¥
	symbols	17.1 (3)	15.8 (4.1)	11.5 (5.7)	<.0001§¥
	time/symbol	5.5 (1.8)	12 (19)	29.5 (33.5)	<0.001§¥
Combined	dual task performance	-1.1 (2)	-10.7 (25)	-287 (563)	<0.005§¥

† significant difference between controls and minimal DAT subgroup

§ significant difference between controls and mild DAT subgroup

¥ significant difference between minimal and mild DAT subgroups

Figure 5.2. Dual task performance for Dual task component of Test of Everyday Attention - visual search with tone counting - for controls and minimal and mild DAT patients, with standard errors



3. Letter fluency

One-way factorial ANOVA was used to analyse the difference in letter fluency for subject group. There was a significant group effect ($F(2,60)=12.4$, $p<0.0001$) (see Figure 5.3) and post hoc analysis showed that mild patients were impaired relative to minimal ($p<0.0005$) and control ($p<0.0001$) groups (i.e. control = minimal > mild).

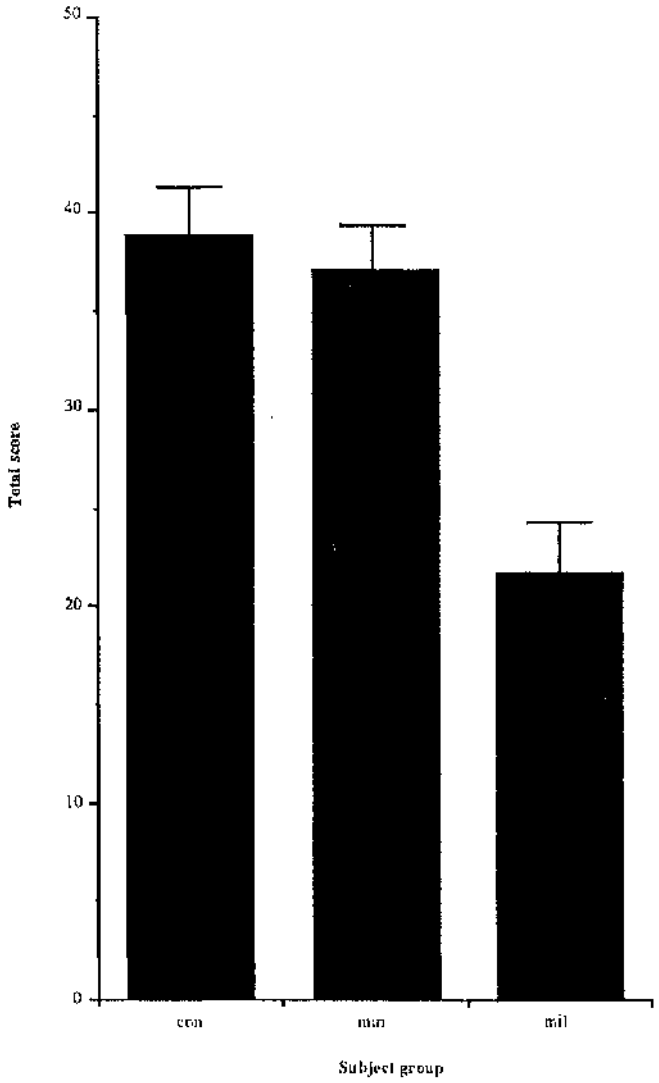
Table 5.3. Performance of the controls and DAT patients on the three measures of frontal function showing mean scores (with standard deviation)

Letter fluency	controls	minimal DAT	mild DAT (SD)	p-values
FAS	39 (13)	37 (9.9)	22 (10)	<.0001§¥

§ significant difference between controls and mild DAT subgroup

¥ significant difference between minimal and mild DAT subgroups

Figure 5.3. FAS letter fluency for controls and minimal and mild DAT patients, with standard errors



In summary, there were significant differences between the controls and DAT patients on a number of measures including the dual-task decrement on both divided attention tests and FAS letter fluency. However, post hoc comparisons showed that only the mild subgroup were consistently impaired. Some of the component scores of the dual performance tasks showed significant impairment in the minimal group (number of boxes filled in the Della Sala *et al* task and time to complete the TEA task): for the calculated dual task performance scores, although the minimal DAT subgroup performed more poorly than controls, these trends were not statistically significant.

Effects of disease on autobiographical memory

The overall performance of the controls and DAT patients on autobiographical memory is shown in Table 5.4.

Table 5.4. Performance on autobiographical tests by minimal and mild DAT patients and controls, with standard deviations

	Controls	Minimal DAT	Mild DAT	p-values
ABF - names	26.8 (10.9)	10.2 (5.2)	7.1 (5.6)	<0.0001†§
ABF - events	16.5 (7.0)	8.2 (5.5)	4.2 (3.9)	<0.0001†§
AMI - pscm	60.0 (3.5)	47.4 (9.1)	41.3 (12.0)	<0.0001†§¥
AMI - incident	21.7 (5.0)	11.6 (6.5)	11.5 (6.9)	<0.0001†§

Key

† significant difference between controls and minimal DAT subgroup

§ significant difference between controls and mild DAT subgroup

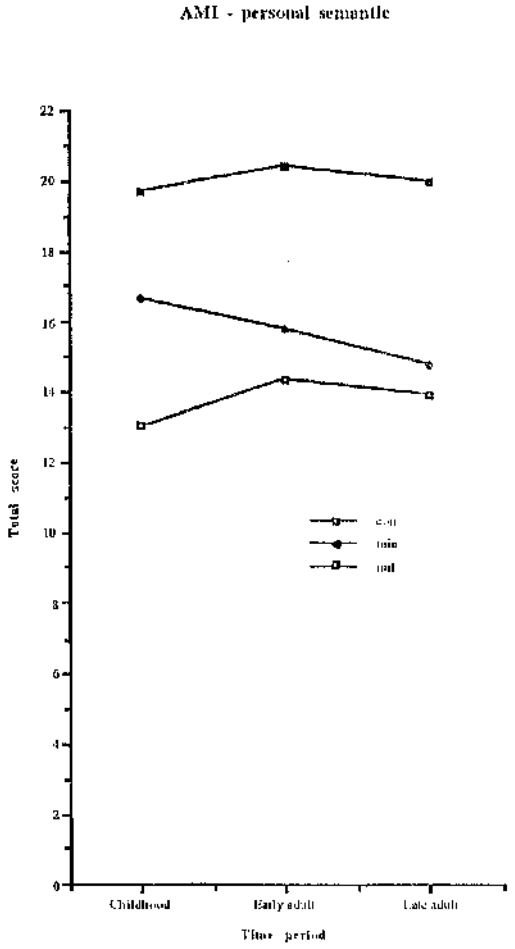
¥ significant difference between minimal and mild DAT subgroups

1. Autobiographical Memory Interview

Personal semantic memory

The Autobiographical Memory Interview data were analysed on the basis of each component. Firstly, personal semantic memory, (e.g. name of school, address prior to wedding), was assessed. Figure 5.4 illustrates performance on the personal semantic component of the AMI by time period. A 3 (groups) X 3 (life periods) ANOVA performed on the personal semantic component of the AMI revealed a significant group difference ($F(2,60)=32.4$, $p<0.0001$). Post hoc analysis showed that controls performed better than both minimal ($p<0.0001$) and mild ($p<0.0001$) groups, but there was no difference between patient groups (i.e. controls > minimal = mild). There was no time period effect ($F(2,120)=0.94$, $p>0.05$), and no interaction ($F(4,120)=1.74$, $p>0.05$). Thus, although both the patient groups were significantly impaired, the degree of impairment appeared equivalent across all three life periods with no evidence of a temporal gradient.

Figure 5.4. Autobiographical Memory Interview - personal semantic component - across three time periods, for controls and minimal and mild DAT patients

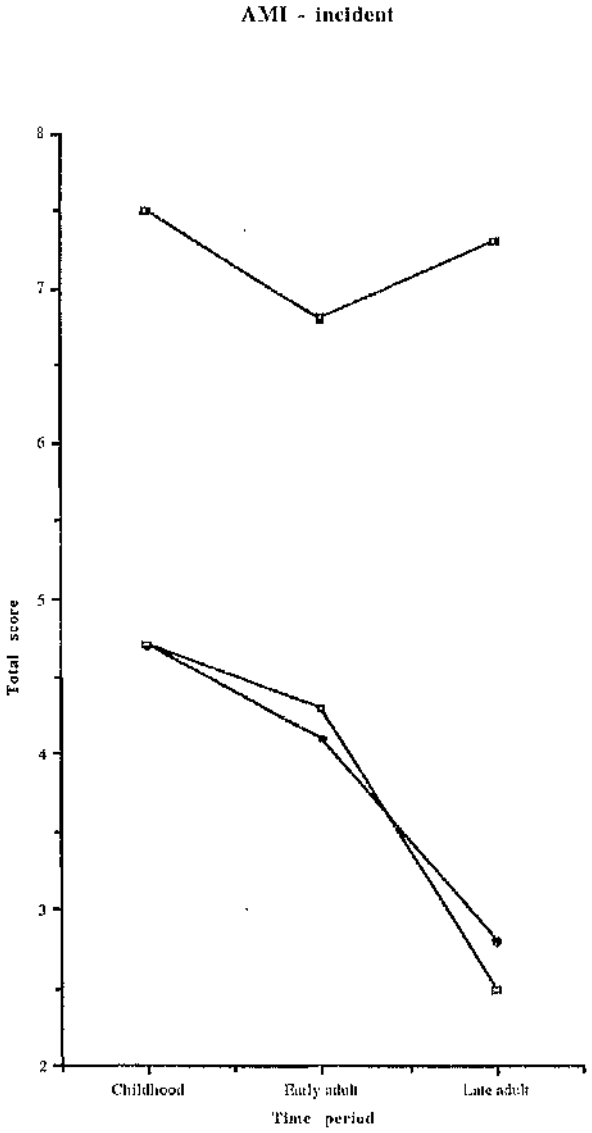


Autobiographical incident memory

For the autobiographical incident component of the AMI (see Figure 5.5), there was also a group effect ($F(2,60)=22.6$, $p<0.0001$) and post hoc analysis again showed that both minimal ($p<0.0001$) and mild ($p<0.0001$) patients performed significantly worse than controls, but that there was no difference between minimal and mild patients (i.e. controls > minimal = mild). But, unlike the semantic component, there was also a time period effect ($F(2,120)=6.0$, $p<0.005$), and a significant group by time period interaction ($F(4,120)=2.93$, $p<0.05$), suggestive of a temporal gradient. One way ANOVA was used to analyse the data for each subject group. Controls performed equally well across the three time periods. For minimal patients there was a trend

towards poorer performance for recent time periods but this fell just short of significance ($F(2,32)=2.80$, $p=0.07$). However, for mild DAT patients, there was a significant time period effect ($F(2,30)=6.07$, $p<0.01$). Post hoc analysis showed that this gradient was due to mild DAT patients performing significantly worse on recent life events compared to childhood ($p<0.005$) and early adult life ($p<0.05$).

Figure 5.5. Autobiographical Memory Interview - incident component - across three time periods, for controls and minimal and mild DAT patients



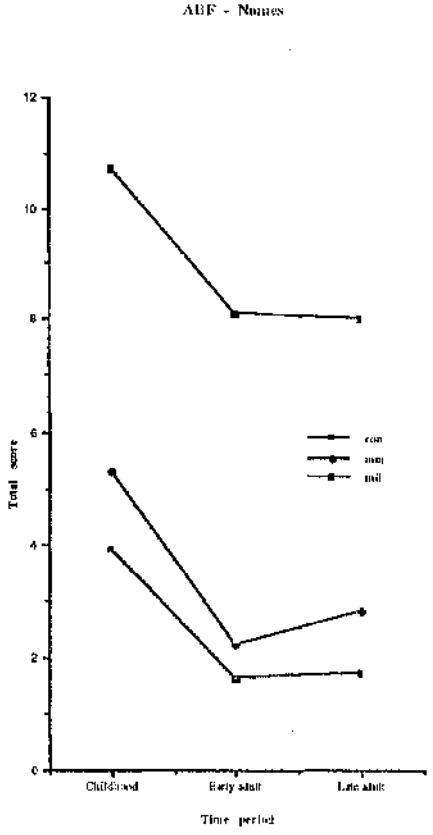
2. Autobiographical fluency

Fluency for names

The results of autobiographical fluency for names are shown in Figure 5.6. I initially considered the results for the three life periods (i.e. childhood, early adulthood, late adulthood) combined. For overall autobiographical name fluency, a one-way ANOVA revealed that there was a significant effect of disease group on performance ($F(2,60)=35.8$, $p<0.0001$). Post-hoc analysis on groups with time periods collapsed showed that both minimal ($p<0.0001$) and mild ($p<0.0001$) patients performed very significantly worse than controls, but that there was no difference between minimal and mild patients (i.e. controls > minimal = mild).

Analysis of performance across the three time periods using a 3 (groups) X 3 (life periods) ANOVA with repeated measures revealed significant effects of group ($F(2,60)=35.8$, $p<0.0001$) and time period ($F(2,120)=13.1$, $p<0.0001$) but no significant interaction between subject group and time period ($F(4,120)=0.10$, $p>0.05$).

Figure 5.6. Autobiographical fluency for names across three time periods, for controls and minimal and mild DAT patients

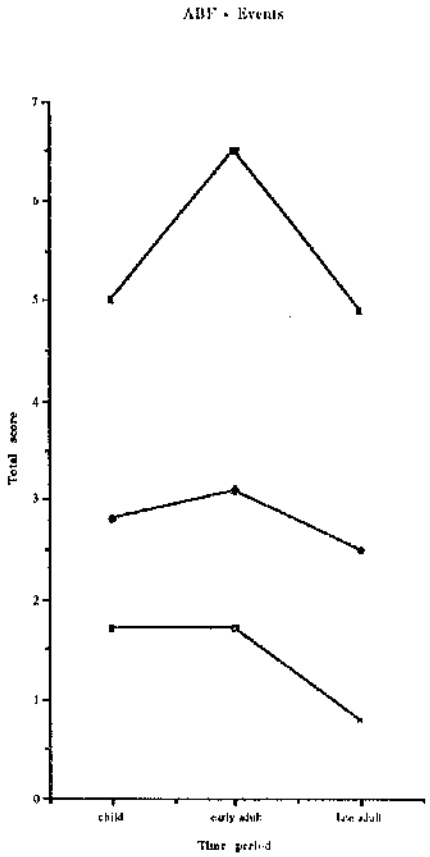


Fluency for events

On overall autobiographical fluency for events, one-way ANOVA revealed that there was a significant effect of disease group on performance ($F(2,60)=24.8$, $p<0.0001$) and post-hoc analysis again showed that both minimal ($p<0.0001$) and mild ($p<0.0001$) patients performed significantly worse than controls, but that there was no difference between minimal and mild patients (i.e. controls > minimal = mild).

To see if there was evidence of a temporal gradient, a 3 (groups) X 3 (life periods) ANOVA with repeated measures was performed. As before, there were significant effects of group ($F(2,60)=24.8$, $p<0.0001$), and time period ($F(2,120)=10.1$, $p<0.001$) (see Figure 5.7). Although there was a trend for mild DAT patients to perform more poorly on late adulthood events suggestive of a temporal gradient, this interaction between subject group and time period fell short of significance ($F(4,120)=1.74$, $p>0.05$).

Figure 5.7. Autobiographical fluency for events across three time periods, for controls and minimal and mild DAT patients



In summary, the minimal and the mild patient groups were impaired with respect to controls on both personal semantic and incident components of autobiographical fluency and the AMI. A temporal gradient was found only for the incident component of the AMI, although there was a trend towards a gradient in the event component of autobiographical fluency.

Consistency of performance across tests of executive function

A correlation matrix for the executive and autobiographical measures indicated that performance on the two dual performance tasks was significantly correlated ($r=0.49$, $p<0.05$) in the DAT group as shown in Table 5.5, but the correlations between these and letter fluency fell just short of significance ($r=0.33$, $p>0.05$ for Della Sala *et al*'s test; $r=0.31$, $p>0.05$ for TEA test).

Table 5.5. Correlation matrix for frontal and autobiographical tests for DAT patients

	DS dtp	TEA	Letter fluency	ABF names	ABF events	AMI psem	AMI abi
DS dtp	1.00						
TEA	0.49**	1.00					
Letter fluency	0.33	0.31	1.00				
ABF names	0.36*	0.36*	0.42*	1.00			
ABF events	0.40*	0.34	0.49**	0.42*	1.00		
AMI psem	0.54**	0.56***	0.44*	0.69***	0.38*	1.00	
AMI abi	0.26	0.24	0.42*	0.29	0.57***	0.52**	1.00

p<0.05 *
p<0.01 **
p<0.001 ***

Key

DS dtp	Della Sala's dual performance test
TEA	Test of everyday attention test
Letter fluency	FAS letter fluency
ABF names	Autobiographical fluency for names
ABF events	Autobiographical fluency for events
AMI psem	AMI - personal semantic
AMI abi	AMI - incident

As shown in Table 5.6, a principal components factor analysis of scores for the two dual performance tasks and letter fluency led to two factors emerging, with the two dual performance tasks emerging strongly in the one factor. On account of this, I felt justified in averaging the z-scores of the two dual performance tasks. ANOVA of the combined dual performance task z-score revealed a group effect ($F(2,60)=6.25$, $p<0.005$), and post hoc analysis showed that minimal DAT patients were normal, but that mild DAT patients were impaired with respect to both controls and minimal DAT patients (con vs. mild, $p<0.005$, minimal vs. mild, $p<0.01$).

Table 5.6. Factor analysis of executive tests

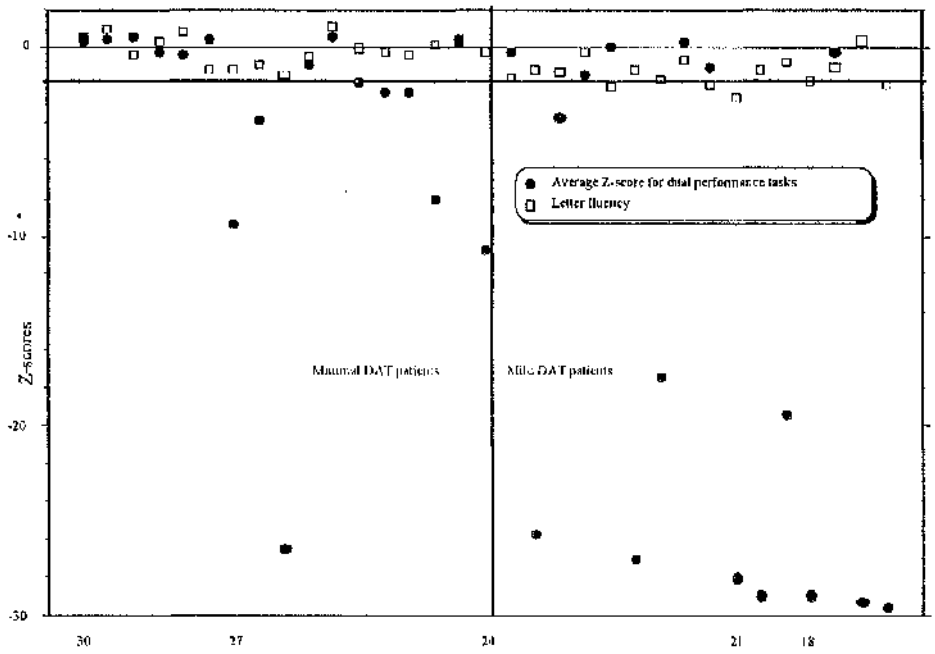
	Factor 1	Factor 2
DS DPT	0.78	0.06
TEA	0.82	-0.01
Letter fluency	0.00	0.94

Key

DS DPT	Della Sala's dual performance test
TEA	Test of everyday attention
Letter fluency	FAS letter fluency

In order to look at the individual DAT patients' performance on the executive tasks, I plotted each patient's Z-scores with the minimal and mild subgroups rank ordered according to their performance on the MMSE (Figure 5.8). It can be seen that 12 of 17 minimal patients' scores fell within the normal range for both dual performance and letter fluency tasks. For the mild group, only 5 of 16 scores fell within the normal range for both tasks.

Figure 5.8. Scattergram of Z-scores for executive tests for minimal and mild DAT patients (Normal cut-off at 1.96 standard deviations as shown)



Consistency of performance across tests of autobiographical memory

As shown in Table 5.5, performance on autobiographical fluency for names correlated significantly with the personal semantic component of the AMI ($r=0.69$, $p<0.001$) and autobiographical fluency for events ($r=0.42$, $p<0.05$). Autobiographical fluency for events correlated with the autobiographical incident component of the AMI ($r=0.57$, $p<0.001$) and to a lesser extent with the personal semantic component of the AMI ($r=0.38$, $p<0.05$). There was a correlation between the two components of the AMI ($r=0.52$, $p<0.01$).

To examine further the relationship between these components, data on the four tasks were entered into a factor analysis (see Table 5.7). The results of the AMI and autobiographical fluency tests were therefore entered into a principal components factor analysis. Two factors emerged: one consisting of autobiographical fluency for names and the personal semantic component of the AMI, (i.e. personal semantic memory). The other consisted of autobiographical fluency for events and the incident component of the AMI, (i.e. incident memory). These results are in keeping with autobiographical memory having two components; a personal semantic component (tested by autobiographical fluency for names and the personal semantic component

of the AMI) and an autobiographical incident component (tested by autobiographical fluency for events and the autobiographical incident component of the AMI).

Table 5.7. Factor analysis of autobiographical tests

	Factor 1	Factor 2
Personal semantic memory	0.72	0.15
Autobiographical incident memory	0.00	0.80
Autobiographical fluency - names	0.86	-0.06
Autobiographical fluency - events	0.04	0.75

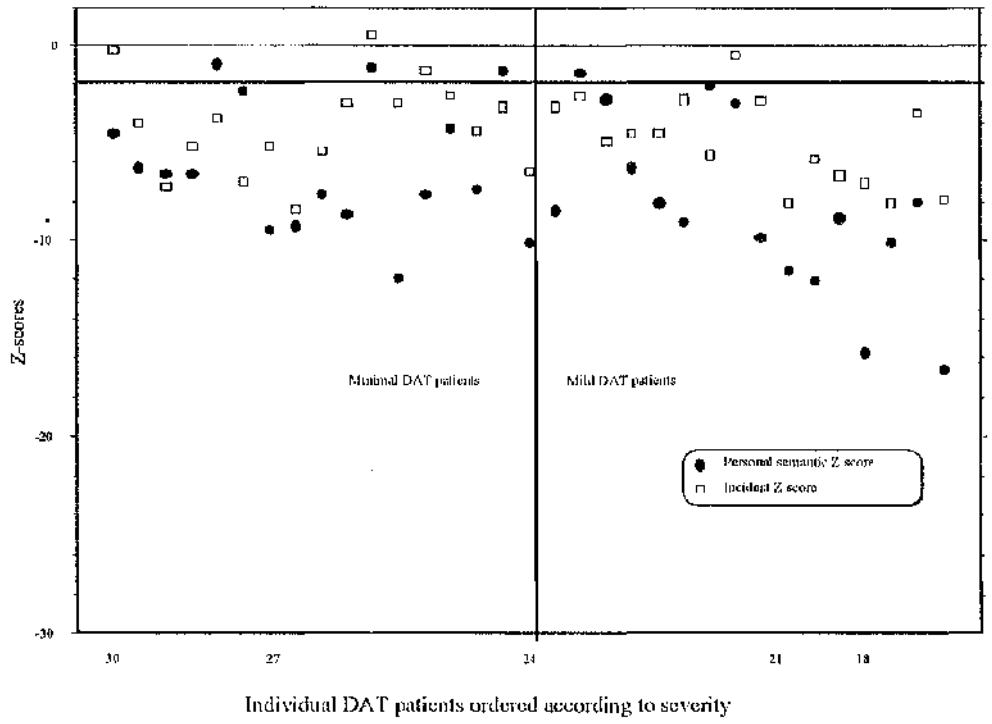
My provision of two tests of autobiographical memory lets me address the issue of the relative contribution of retrieval impairment and storage loss to autobiographical memory. Verbal fluency tests (which do not provide specific cues for a response) depend on the integrity of retrieval processes and of memory stores, while tests which provide very specific pointers, as in the AMI, place less demands on retrieval operations. A contrast between performance on these two tests of personal semantic memory might reveal whether subjects have a predominant retrieval disorder (i.e. a deficit in retrieving information in open-ended tasks with improved performance on tests providing specific cues) or a loss of storage (impaired performance on open and closed tasks).

Figures 5.3 and 5.4 suggest that DAT subjects have both a retrieval disorder, since subjects do relatively better in the AMI test than the verbal fluency test, and a loss of storage, since even with specific cues performance is worse than controls. Assessment of individual cases, however, revealed some cases with predominantly a retrieval disorder (i.e. impaired fluency with normal performance on the AMI), whereas in others a storage disorder was the main deficit.

Having established that patients with minimal and mild DAT show impairment on a range of autobiographical memory tasks, I wanted to examine further whether these statistically significant findings reflected a general decline in the majority of cases or a more marked impairment in a smaller cohort of patients. On the basis of the above factor loadings, I averaged the z-scores of AMI personal semantic memory and autobiographical fluency for names to obtain measures of personal semantic, and did likewise with AMI incidents and autobiographical fluency events for incident memory. Figure 5.9 shows the performance of the individual patients in the minimal and mild DAT sub-groups (based on their z-scores) on the personal semantic and incident components of autobiographical memory. The patients have been ordered by level of global cognitive performance as judged by their performance

on the MMSE. It can be seen that only 1 of 17 minimal, and none of 16 mild DAT patients scored normally on both personal semantic and incident memory.

Figure 5.9. Scattergram of Z-scores for autobiographical tests for minimal and mild DAT patients (Normal cut-off at 1.96 standard deviations as shown)



Figures 5.5 and 5.6 together illustrate that autobiographical memory becomes impaired in DAT early in the disease while executive function becomes consistently impaired principally in more established cases.

Relation between executive function and autobiographical memory

Although there were many intercorrelations between the three executive tests and the four measures of autobiographical memory, I wished to further address the role of executive function in autobiographical memory.

The four measures of autobiographical memory were first entered into a factor analysis which yielded two factors, one of personal semantic memory and one of incident memory (as detailed above). These two autobiographical factors were then each used as a dependent variable, and the two dual performance tasks and letter fluency were used as independent variables in a regression analysis. I hoped to see

which aspects of executive function contributed to the personal semantic and incident components of autobiographical memory.

Firstly I attempted to create a stepwise regression model which would predict personal semantic memory using incident memory and the three executive tests. For each step, each variable was tried in the regression, and the one which best predicted the dependent variable as measured by R squared was added. At the next step, the remaining independent variables were each tried in turn, and the equation was thereby built up. Stepwise regression models were created in which executive tests were used as predictors for both personal semantic and incident memory. Incident memory was the best predictor of personal semantic memory, and could account for 22% of the variance. Each executive test was then added to this model. The TEA test accounted for a further 21% of the variance. Subsequent addition of the DPT accounted for a further 6% of the variance. Letter fluency added another 6%. Thus, the factors which could predict personal semantic memory were, in decreasing order of importance, incident memory, the TEA test, the DPT and letter fluency. Together this model could account for 56% of the variance in personal semantic autobiographical memory.

A similar analysis was done for incident memory. Personal semantic memory was the best predictor of incident memory, accounting for 22% of the variance. The addition of letter fluency to the model added a further 21%. The DPT added a further 6%, and the TEA test a further 1% of the variance. Thus 50% of the variance in incident memory could be explained by a regression model including the following factors in decreasing order of importance: personal semantic memory, letter fluency, DPT and the TEA test.

These results show that performance on either component of autobiographical memory is more dependent on the other component of autobiographical memory than on executive tasks. Personal semantic autobiographical memory performance can be best predicted by incident autobiographical memory and the dual performance tasks, while letter fluency plays a lesser role.

Incident memory is likewise heavily dependent on personal semantic memory. In contrast to personal semantic memory, however, letter fluency strongly predicts incident memory, and the dual performance tasks are of lesser importance.

I have shown, therefore, that personal semantic memory is dependent on the component of executive function measured by dual performance tasks. Incident memory, by contrast, is more dependent on verbal fluency tests rather than on dual performance tests.

Discussion

My results have confirmed that autobiographical memory and executive function are impaired in DAT, but at different stages of the disease: patients defined as having minimal DAT showed deficits on both measures of autobiographical memory, but were not significantly impaired on the executive tasks, while patients with more established disease (mild DAT subgroup) showed impairment on all autobiographical and executive tests. I shall now address the various points raised in the introduction.

Is Autobiographical memory consistently impaired early in the course of DAT?

Analysis of group data showed that both minimal and mild DAT patient groups were impaired on autobiographical memory with respect to controls. I found that this applied to both personal semantic and incident components of autobiographical memory. That autobiographical memory is impaired in DAT is in keeping with previous studies [78, 185, 188, 280]. Of these studies, only Kopelman addressed both personal semantic and incident memory. He, like me, found both to be impaired. Most previous studies have, however, treated DAT patients as a single group, with the exception of Dall'Ora *et al* [78]. By stratifying the patient group, I have shown that autobiographical memory is impaired even in the minimal group, who have MMSE scores of 24 and above. This is perhaps somewhat surprising since it is commonly believed that DAT spares remote memory in the early stages of the disease. The finding of impaired autobiographical memory very early in the course of DAT implies that structures beyond the hippocampus are involved by the time patients present. This conclusion is based on the fact that pathology confined to the CA1 zone of the hippocampus appears to produce a pure anterograde deficit, while damage to parahippocampal and/or diencephalic structures almost invariably results in a combined anterograde and retrograde amnesia [140, 308]. Current neuropathological evidence suggests that the transentorhinal region bears the brunt of the pathology in early Alzheimer's disease [42, 335, 336] which would be expected to be associated with a combined anterograde and retrograde deficit, as shown in this study.

Within the patient groups, however, there was marked heterogeneity in autobiographical memory performance, reflecting perhaps the variation in anatomical structures affected by Alzheimer pathology.

Is there evidence of a temporal gradient for autobiographical memory?

The tests used assessed both personal semantic and incident components of autobiographical memory, using fluency and the AMI. There was no evidence of a temporal gradient for personal semantic memory in either test. In contrast, for

autobiographical incident memory there was a temporal gradient present in the AMI. The event component of the autobiographical fluency test tended towards a temporal gradient, but not significantly. This finding may reflect greater sensitivity of the AMI as a test of remote memory. Also, the fluency task stresses general speed of cognition, in addition to autobiographical memory retrieval; the effect of speed of cognition is likely to apply across all time periods, and thus may mask the gradient in autobiographical incident memory apparent in the AMI. This gradient was present for both patient groups, but was significant only in the mild patient group. Recall of incidents from late adulthood was significantly poorer than from childhood and early adulthood. It should be noted that although statistically significant, this was only a gentle temporal gradient. The finding of a very mild gradient is in keeping with recent findings when analysing remote memory using tests of famous face identification [148].

My finding of a temporal gradient for autobiographical incident memory, but not for personal semantic memory, provides partial support for the separability of these components within autobiographical memory. Autobiographical incident memory has all the features of episodic memory: a specific personal incident is time- and context-specific and has to be reconstructed. Personal semantic memory, by contrast, is perhaps more similar to general semantic memory.

It is interesting to speculate on the possible neural and cognitive underpinning of the temporal gradient. One possible explanation is that the apparent gradient is an artefact due to difficulty dating the insidious onset of DAT. Initial DAT pathology may develop some time before clinical presentation. Therefore what is considered recent remote memory may in fact refer to a time period after the onset of pathology and therefore be anterograde episodic memory. If this were so, however, I would expect to see the gradient in all four components of the autobiographical tests, which is not the case.

Another possible explanation of the temporal gradient relates to the status of autobiographical memories of differing time periods within the episodic-semantic spectrum. It is felt that memories from the most recent decades are truly "episodic", in that temporal and contextual cues are utilised in their retrieval [64]. More distant memories, by contrast, have been retrieved more repeatedly, thereby losing temporal and contextual specificity and acquiring features of semantic knowledge. Semantic memories may rely less on the limbic system for retrieval. The perihippocampal pathology seen in early DAT will impair episodic recent autobiographical memories, but distant, more "semantic", memories will be relatively spared, possibly accounting for the temporal gradient.

My finding of a temporal gradient for autobiographical incidents is in keeping with the results of Kopelman [188]. Dall'Ora *et al* [78], however, using an autobiographical memory enquiry (which only assessed incident memory), found no such gradient. One possible explanation for this finding is that they did not stratify their DAT group, and any gradient present in less severe patients may have been masked by this pooling. Kopelman [185], however, felt that the lack of gradient in Dall'Ora *et al*'s study may have been a test artefact, due to the differing time-periods in the two tasks within which subjects were constrained to produce 'recent' memories (1-5 yrs in Dall'Ora *et al*'s study versus 15 yrs in the AMI).

Unlike the present study, Kopelman [188] found evidence of a temporal gradient for the personal semantic component as well as the incident component of the AMI. This could be due to a difference in severity of DAT between my patients and Kopelman's. It is difficult to verify this, as Kopelman did not report MMSE data. The level of performance of his patients on the logical memory test suggests, however, that they performed at a level intermediate between my minimal and mild groups. Another explanation might be due to my alteration of the "recent life" component of the AMI. I deliberately modified the test to shift the time-frame back, in an attempt to assess truly remote memory. The existing AMI, by asking about recent hospital visits and last Christmas etc. is, I feel, more likely to be assessing anterograde memory. The original version of the AMI may have caused a spurious temporal gradient for personal semantic memory by incorporating anterograde memories, which are impaired early in DAT.

Is the central executive component defective in early DAT patients ?

Executive function was assessed by letter fluency and the two dual performance tasks, which stress the central executive component of working memory. Patients in the earliest stages (designated minimal) of DAT differed significantly from controls on two of the individual component measures of the dual performance tests (boxes filled in Della Sala *et al*'s test and time to complete the TEA test) but showed no overall impairment on either the combined dual-performance or letter fluency. Mild patients, however, were impaired on all measures.

Previous studies have shown deficits in frontal executive and working memory in DAT [14, 185, 188] but have failed to subdivide their DAT patients on the basis of disease severity; the combination of patients with minimal and mild disease could lead to the conclusion that central executive deficits are present from very early in the course of DAT. Another potential reason for the difference between my study and that of Baddeley *et al* [14] relates to task design. My task utilised box filling and simultaneous repetition of digit span sequences. Baddeley *et al* employed tracking a

white square on a computer screen with a light pen while repeating digit span sequences. Their patients performed more poorly on both tasks in the dual task condition. My patients, by contrast, performed more poorly on the box filling, but maintained their performance on the digit span sequences. It seems unlikely, however, that this change in methodology by itself accounts for the relatively unimpaired performance of the minimal DAT subgroup as they were also not significantly impaired on the other dual task (TEA test) used in the present study.

A possible explanation of my finding of relative sparing of executive function in minimal DAT could be related to my method of classification using the MMSE. It might be argued that the MMSE, in part, measures executive function. A patient with intact executive function will score higher on the MMSE, and therefore will be more likely to be classified as minimal than one with impaired executive function. The finding of intact executive function in minimal DAT might therefore be an artefact as a result of defining my DAT patients in terms of severity. It is true that the orientation and attention components of the MMSE do rely on executive function to some extent. However, patients with established frontal pathology often perform normally on these components of the MMSE, indicating that these are relatively insensitive tests of executive dysfunction [125]. I, therefore, feel that the sparing of executive function in minimal DAT is genuine, and is not an artefact of classifying disease severity.

Another possible confounder is that my DAT group has been diagnosed primarily on the basis of memory impairment. Within the heterogeneous DAT population, I have essentially selected out the subset of DAT patients who present with memory impairment. These patients are likely to have pathology which initially affects the perihippocampal region. Admittedly this is by far the commonest presentation of DAT. There is, however, accruing evidence for the heterogeneity of DAT in terms of its initial presentation; histologically confirmed cases of AD may present with aphasia [32, 123, 179, 259], visuo-spatial and perceptual disturbances [151, 183, 199, 277] or apraxia [74]. My means of diagnosing DAT may be selecting those patients with perihippocampal pathology and impaired episodic but preserved executive function, thus accounting for the apparent sparing of executive function in early DAT. Although there have been no neuropathologically confirmed cases of DAT presenting with a purely dysexecutive syndrome, it remains possible that this could occur. Should this be the case, my sample would not be representative of the minimal stages of DAT in general.

To be a measure of central executive function, the single task component of a dual-task should be performed equally well by patients and controls. On one of the dual-tasks used in the current study, from the Test of Everyday Attention [274], the patients were impaired on the single task. This implies that the TEA is less pure in

terms of testing executive function. Della Sala *et al*'s dual performance test, by contrast, has been devised specifically to assess central executive function. In this latter test, the two single tasks were performed equally well by patient groups and controls. A final methodological point concerns the sensitivity of the dual performance tasks employed. Since the minimal DAT subgroup showed a consistent trend towards impaired performance, and were indeed significantly impaired on two subcomponents of the tests, it is possible that more stringent executive tests would demonstrate a significant dual task decrement. Examination of Tables 5.1 and 5.2 show, however, that the controls were not performing at ceiling and showed considerable variance in performance, suggesting that the executive tests are sufficiently sensitive to detect subtle impairments.

Despite the above caveats, I feel that executive function is genuinely spared in minimal DAT, at least in the majority of cases. This conclusion is in keeping with the study of Sahakian *et al* [281] who also found sparing of executive function in a group of patients with early DAT. They employed a test of visual selective attention and intradimensional/extradimentional shift from the CANTAB battery [273, 283]. The preservation of working memory in minimal DAT is also in keeping with neuropathological studies which report that the frontal lobes are affected by Alzheimer pathology only in more established disease [42, 336], by functional imaging studies showing hypometabolism in the temporo-parietal association cortices early in the disease, with frontal hypoperfusion only appearing in more established disease [97, 110, 112], and by other neuropsychological studies showing that minimal DAT patients have neuropsychological deficits consistent with predominantly posterior cortical rather than frontal pathology [284].

What is the relationship between executive and autobiographical memory in DAT ?

Executive function, it has been suggested, may be involved in both storage and retrieval of autobiographical memories [91]. The quality of the new memory will be dependent on attentional factors. Once learned, the retrieval of an autobiographical memory requires the active process of recollection and verification. Executive impairment may lead to a poorer search and recollection process, and hence impaired retrieval of autobiographical memories [90]. As I am here concerned with the retrieval of autobiographical memories which occurred prior to the onset of Alzheimer pathology, I am only addressing the relationship between executive function and the retrieval of autobiographical memory.

I found limited evidence that executive function is implicated in the retrieval of autobiographical memory. All three executive tasks correlated with at least some

components of autobiographical memory; the personal semantic component of the AMI correlated most with executive tasks, and to a lesser extent with letter fluency, while the incident component correlated only with letter fluency. It is surprising that executive function appears to correlate more with the personal semantic rather than incident component of autobiographical memory. As stated in the Introduction to this chapter, current theoretical models propose a role for frontal-lobe executive functions in the retrieval, reconstruction and verification of autobiographical events and I had, therefore, predicted a closer correlation between executive tests and incident memory.

Stepwise regression provided further limited support for the executive-autobiographical link. For the personal semantic component of autobiographical memory, an analysis using autobiographical incident memory and the three executive tests could predict 56% of the variance; incident memory was a better predictor of personal semantic memory than any of the three executive tests. A similar analysis using personal semantic memory and the three executive tests could predict 50% of the variance in incident memory. Again the complementary component of autobiographical memory (in this case personal semantic memory) was a better predictor of incident memory than any of the executive tests.

However, the finding of impaired autobiographical memory in minimal DAT - in the context of relative preservation of executive functional level - suggests that the role of executive function in autobiographical memory retrieval is limited, or alternatively that the deficit in autobiographical memory found in DAT is due to a loss of memory stores rather than breakdown in retrieval processes (see below). Review of the previous literature on this topic provides no clear consensus view. Della Sala *et al* [90, 91] produced evidence for the role of executive function in the retrieval of autobiographical memory, and Kopelman [185] found that frontal function correlated with autobiographical retrieval. He also claimed that combined frontal dysfunction and limbic-diencephalic pathology are necessary to produce a temporally-extensive retrograde loss, as isolated frontal lesions affect memory to only a limited extent [288, 318]. On the other hand, Kopelman [188] and Dall'Ora *et al* [78] found little evidence of association between frontal atrophy and function and autobiographical memory, and remote memory impairment has been detected in the absence of frontal dysfunction [24, 27, 285, 311].

It might be argued that my finding of impaired autobiographical memory but preserved executive function in minimal DAT is simply due to my executive tests being less sensitive. However, the controls were not performing at ceiling on executive tasks. If anything, it is on the AMI that ceiling effects in controls are observed.

The conclusion that loss of autobiographical memory traces, rather than defective retrieval, may be a more important factor is supported by the relative

pattern of performance on the two tests of autobiographical memory which have arguably different retrieval demands. Impaired executive function will lead to poorer search and reconstruction processes, which will result in impaired retrieval of episodes. If the deficit is predominantly one of retrieval, then administration of more constrained cued questions, as in the AMI, should lead to a significant improvement over more open tests such as autobiographical fluency. If the autobiographical impairment is due to degradation of the individual memory traces constituting autobiographical memory, then the deficit should be present in both tests. From my results it seems probable that both loss of storage and retrieval deficits are contributing to the autobiographical impairment.

The neural basis of long-term memory is still poorly defined, but as discussed in the Introduction it seems likely that posterior association cortices play a major role in the storage of the elements which constitute autobiographical memory [81, 141]. Thus, the hypothesis that loss of such stores occurs in DAT is in keeping with functional imaging studies [97, 110, 112] which show characteristic temporoparietal deficits in early DAT, but with preservation of frontal cortex until later in the disease. Given the heterogeneity in the neuroanatomical spread of DAT, it would not be surprising if some of my patients showed primarily a loss of storage, while others had primarily a retrieval deficit. Clearly further studies are required to address the relative contribution of these deficits in DAT.

Are there subcomponents within autobiographical memory and within executive function?

My results also provide evidence in support of the fractionation of both autobiographical memory and executive function. The finding of a temporal gradient for autobiographical incident memory but not for personal semantic memory argues for a fractionation of autobiographical memory. This contention was supported by the results of factor analysis of the four measures of autobiographical memory (autobiographical fluency for names and events, and the personal semantic and incident components of the AMI) which yielded two factors, corresponding to personal semantic and incident memory. Analysis of the executive measures led to a similar conclusion regarding the fractionation of executive function: the mechanisms underlying performance on dual-task and verbal fluency appear to be distinct.

Further support for separable divisions within both autobiographical memory and executive function comes from the finding that certain executive tasks which measure divided attention, i.e. dual task performance, were of most use in predicting personal semantic memory. By contrast, incident memory could be best predicted by letter fluency. The fact that some personal semantic autobiographical tests used in

this study ask specific questions while no tests of incident memory did so, may partially explain why incident memory correlated more closely with verbal fluency than did personal memory. It appears therefore that these two components - semantic and incident memory - represent subdivisions which I assume have separate neural bases yet to be fully explored.

One can only speculate why this double dissociation between type of executive function and type of autobiographical memory occurs. Retrieval of a personal semantic memory involves active search mechanisms to locate, retrieve and verify a unique item. This process may share elements of processing in common with the divided attention strategies needed in the dual performance tasks. The retrieval of an autobiographical incident (e.g. memory from childhood) does not necessitate a search for a particular episode. Instead, once a memory which fulfils the criteria is found, the subject is required to elaborate to give a rich evocation of the memory. This may involve a general fluency measure which might also be shared by those processes utilised in letter fluency.

Although my test results seem to demonstrate two components of executive function, there may well be other aspects of executive function not tapped by my divided attention and fluency tasks which play a more crucial role in the retrieval of autobiographical memory.

Summary

I studied executive function and autobiographical memory in a cohort of 33 DAT patients [divided into minimal (MMSE 24-30) and mild (MMSE 17-23) groups] and in 30 normal controls. Autobiographical memory, as assessed by autobiographical fluency and the Autobiographical Memory Interview (AMI), was impaired in DAT patients, even those with minimal disease. There was evidence of a gentle temporal gradient on the incident but not the personal semantic component of the AMI, suggesting that the two components are dissociable. Executive function was assessed by two separate dual performance tasks and letter fluency. Although there was a trend for minimal DAT patients to be impaired on executive tasks, this only reached significance for the mild group. Regression analysis suggested that the divided attention component of working memory was involved in the retrieval of personal semantic autobiographical memory, but verbal fluency was more important in the retrieval of autobiographical incidents. There was thus a dissociation in the type of executive function implicated in different subcomponents of autobiographical memory, arguing for subcomponents within executive function and autobiographical memory. The autobiographical memory deficit in DAT reflects, I suggest, both

impairment in retrieval processes, linked to executive function, and a loss of memory stores.

Chapter Six

Analysis of the episodic memory deficit in early dementia of Alzheimer type: Evidence from the Doors and People Test

Introduction

This chapter deals with the anterograde episodic memory found almost universally in patients with early DAT, and addresses the relative contributions of impaired encoding, storage and retrieval of new information using both well established tests of verbal memory, and the newly developed Doors and People Test.

It has been argued that the anterograde episodic memory deficit in DAT is primarily the result of poor encoding [88, 122, 175, 211, 347, 349, 359], although there is also evidence of increased sensitivity to pro-active interference [56, 58, 88, 187]. Weingartner *et al* found that DAT patients fail to use information about how events are related to one another in order to learn more effectively and organise memories, even on tasks that make little demand on sustained motivation and effort [348, 349]. This may be exacerbated due to inability to access semantic memory structures that are necessary for the rich encoding of information. Weingartner *et al* [349] observed that learning and recall were not facilitated by repeated presentation, by repeating forgotten information, by providing sequential organisation or by using stimuli that are semantically related, a pattern of results they interpret as suggesting impaired encoding in DAT patients. Granholm and Butters [122], using an encoding-specificity paradigm, also found that DAT patients either are impaired in their ability to encode the semantic relationship between a word and its retrieval cue or are unable to utilise the product of encoding at the time of retrieval. Delis *et al* [88], using the California Verbal Learning Test, found that Alzheimer patients displayed severely impaired immediate recall, flat learning rates across trials, inconsistent recall across trials, ineffective use of semantic clustering, a tendency to recall words passively from the recency region of the list, poor retention over delay intervals, high intrusion rates, poor recognition discriminability, high false positive rates, a mild "Yes" response bias, and no improvement on recognition testing relative to free recall (suggesting predominantly an encoding and storage impairment).

In summary, several studies have shown very poor learning in DAT patients, coupled with a failure to benefit from encoding operations that enhance learning in both normal subjects and in many brain-damaged patients. This pattern of results suggests a failure to benefit from richer (or enhanced) encoding, indicating a deficit in the encoding processes and/or a failure to store the memory trace resulting from such encoding operations.

The question of whether patients with DAT show a normal or accelerated rate of forgetting remains much more controversial. While most studies have claimed that the forgetting rate is accelerated in DAT [59, 130, 195, 239, 352], some have claimed that DAT patients show normal forgetting [26, 186, 187, 227].

There are two approaches to studying the forgetting rate in DAT. One is to allow the DAT patients extra trials or time to acquire new information, thus equating acquisition in DAT patients and controls. Kopelman [187], after equating performance at 10-minute delay, found that the forgetting rate, as tested at 24 and 72 hours, was normal. Corkin *et al* [72], after matching performance at 10 minutes post-presentation, found that forgetting was poorer in DAT at 24 hours, but was no different from controls at 72 hours. Hart *et al* [130], after matching performance at 90 seconds, found accelerated forgetting at 10 minutes, but not at 2 or 24 hours. These tests used recognition rather than recall.

Another approach is to give the same number of learning trials to patients and controls; this results in DAT patients learning less. The absolute difference between items learned and items recalled after an interval can be used as a measure of forgetting. Using this method, Becker *et al* [26] found that the forgetting rate for DAT patients was no different from controls, for both verbal and nonverbal material. By contrast, Moss *et al* [239], using proportion of items recalled at 15 seconds which were still retained at 2 minutes, found accelerated forgetting of verbal material. Larrabee *et al* [195], using the difference between immediate recall and delayed recall over 30 and 40 minutes, found evidence of accelerated forgetting. Even when subsets of DAT patients and controls who showed equivalent learning were selected, the DAT subgroup was found to show accelerated forgetting when compared to the control subgroup.

The varied conclusions regarding whether forgetting in DAT is normal or accelerated may be due to methodological factors, or be due to the time period during which retention is tested. In general, studies using proportion retained as a measure of forgetting tend to show increased forgetting in DAT [239], while those using absolute measures of loss of information tend to show normal forgetting [26].

The interpretation of forgetting functions is therefore fraught with problems (see [214] for a discussion). Loss of information between immediate and delayed recall may represent either of two factors. The first reflects the contribution of working memory to immediate, but not delayed, recall, as shown for example in the role of the recency effect in immediate free recall. The second factor represents the loss of information from long-term memory, which in turn may, or may not, be influenced by level of initial learning [204, 299].

A further possible source of memory deficit in DAT patients could be a result of impairment at the retrieval stage. While it is far from easy to produce a clear separation between the effects of encoding and retrieval, a major differential disruption of one of these stages can be detected by contrasting recall and recognition performance. Whereas the classic amnesic syndrome produces memory deficits on

both of these measures, Huntington's disease produces a pattern in which recall is typically more impaired than recognition [44, 146, 278], an effect that is attributed to the differential disruption of the retrieval component necessary for adequate recall. A major methodological problem in this area stems from a tendency to use tests of recall and recognition that are not adequately standardised, leading to problems of interpretation (see [296] for a discussion). It is, therefore, important to use tests providing standardised scores that allow recall and recognition measures to be compared.

A similar problem of cross-test comparability also complicates the claims for a degree of material-specificity in DAT patients. It has been suggested that DAT may affect the left hemisphere preferentially [113, 132, 191, 203, 262], which might be expected to produce a degree of material-specificity with greater disruption of verbal memory. Although most DAT patients show substantial impairment in both verbal and nonverbal memory, there are suggestions that the deficit may be material-specific early in the disease, at least in a proportion of cases [15, 212]. While material-specificity may be due to the coexisting presence of other cognitive deficits [94, 210-212], at least some patients with early DAT appear to show material-specific memory impairment. Becker *et al* [29] report evidence of material-specific loss in 13% of their patients, based on a study in which verbal memory was assessed by immediate and delayed recall of a short story [346] and nonverbal memory by recall of the Rey-Osterreith figure [251, 269]. However, interpretation is complicated by the question of whether the two measures are comparable in difficulty, and whether the contribution of non-mnemonic factors such as semantic coding or working memory is equivalent. Finally, the fact that the two tasks were presented using different modalities confounds material-specificity with modality-specificity.

The study that follows uses three tests of memory to analyse the nature of the episodic memory deficit found in DAT patients. My first measure involved the immediate and delayed recall of a verbal passage, a classic measure that is known to be sensitive to the disease, and which has been claimed to show greater forgetting in DAT patients [327]. The second measure involved the CERAD word list which was developed specifically for the study of learning and forgetting in Alzheimer's disease. Since it involves repeated trials of immediate recall, delayed recall and recognition, results should bear on the nature of the learning deficit, the rate of forgetting and on the role of retrieval as reflected by differential recall and recognition deficits. The third measure was the Doors and People test recently developed by Baddeley, Emslie and Nimmo-Smith [16]. This test yields an overall episodic memory score which can be decomposed into a range of subscores, each based on a minimum of two subtests, which being based on scaled scores can be combined to yield a number of standardised

indices. The possibility of a specific retrieval deficit can be measured by comparing recall and recognition scores, while visual and verbal measures allow for a test of material-specificity. The recall measures, involving three successive learning trials, followed by delayed recall, provide standardised measures of both learning and forgetting.

Finally, in addition to my attempt to analyse the nature of the episodic memory deficit in DAT, my study was concerned with the practical problem of developing measures capable of monitoring the stages of progression of disease. In order to do this, I divided the patients into two subgroups on the basis of their Mini-Mental State Examination (MMSE) score. For a measure to be useful in staging, it should not only be sensitive to DAT, but should also be capable of differentiating between patients at a very early stage of the disease, as reflected by a minimal deficit (MMSE range 24-30), and more advanced cases with a mild deficit (MMSE 17-23).

It is not certain that these tests are equivalent in difficulty, or that the contribution of non-mnemonic factors such as semantic coding are equivalent.

In summary, to study anterograde recall and recognition memory for verbal and nonverbal material in early DAT I used two established tests and the Doors and People test. The aims were i) to examine the learning rate in DAT, ii) to study forgetting in DAT, iii) to use recall and recognition measures to address the issue of whether the episodic memory impairment in DAT is due to failure of encoding, storage or impaired retrieval, iv) to see if any of my patients with early-stage DAT exhibited material-specific memory impairment, and v) to see if any of the memory measures were of use in staging DAT severity.

Methods

Subjects

The following data were collected from 33 DAT patients and 30 controls on testing at year 1. Fuller details of the subject groups, and the tests used, are given in Chapter 2.

Tests

The tests employed here are described in Chapter 2.

Results

The overall performance of the controls and DAT groups on the anterograde memory tests is shown in Tables 6.1, 6.2 and 6.3.

Logical memory

As shown in Table 6.1, both the minimal and mild DAT groups were markedly impaired on the immediate and delayed recall components of the logical memory test. Comparison of the groups' performance on the immediate recall component by one-way ANOVA revealed a significant main effect ($F(2, 60)=49.2$, $p<0.0001$); post hoc pairwise comparisons showed that there were significant differences between controls, minimal and mild DAT patients (i.e. controls > minimal > mild; con vs. min $p<0.0001$, con vs. mild $p<0.0001$, min vs. mild $p<0.05$). For delayed recall, an ANOVA also revealed a significant group difference ($F(2, 60)=90.1$, $p<0.0001$), with post hoc analysis showing that DAT patients were impaired with respect to controls, but there was no difference between patient groups (i.e. controls > minimal = mild; con vs. min $p<0.0001$, con vs. mild $p<0.0001$, min vs. mild $p>0.05$).

To assess amount of forgetting, I performed a 2 (immediate and delayed recall) x 3 (groups) ANOVA which showed significant main condition ($F(1,60)=128.4$ $p<0.0001$) and group effects ($F(2,60)=74.1$, $p<0.0001$) and a group by condition interaction ($F(2,60)=14.5$, $p<0.0001$). Post hoc pairwise comparisons indicated that the amount of forgetting was greater in both patient groups than in controls ($p<0.0001$ for each patient group vs. controls), but that there was no difference between patient groups ($p>0.05$).

Table 6.1. Performance of controls, minimal and mild DAT patients on the Logical Memory test; Scaled scores given (standard deviations in brackets)

		Controls n=30	Minimal DAT n=17	Mild DAT n=16	p-values
Logical Memory Score (Max = 47)	Immediate recall	9.9 (2.8)	4.8 (2.1)	3.0 (2.0)	<0.0001†§¥
	Delayed recall	8.8 (3.0)	1.4 (1.9)	0.5 (0.8)	<0.0001†§

† significant difference between controls and minimal DAT subgroup

§ significant difference between controls and mild DAT subgroup

¥ significant difference between minimal and mild DAT subgroups

Comment

While control subjects show the characteristic pattern of minimal forgetting on this test, both DAT groups showed poor immediate recall and virtually no recall after the delay. I therefore replicated the differential forgetting reported by Troster *et al* [327]. This result might possibly reflect more rapid loss of information from long term

memory in DAT patients, but it is equally possible that it reflects the contribution of working memory to the immediate recall performance of the DAT patients, a contribution that would be dissipated in all groups by the intervening delay. It is notable that even densely amnesic patients are capable of showing above average performance on the immediate recall of a prose passage, while demonstrating a virtual total absence of long term learning [357]. Evidence on which of these two interpretations is more plausible comes from the study of forgetting across the two subsequent tests.

CERAD word list

The results on the CERAD word list are shown in Table 6.2.

Table 6.2. Performance of controls, minimal and mild DAT patients on the CERAD word list. Scores are scaled, with 10 representing the average score for normal subjects.

		Controls n=30	Minimal DAT n=17	Mild DAT n=16	p-values
CERAD word list					
	Immediate recall (max = 10)	7.6 (1.3)	4.5 (2.0)	3.4 (1.6)	<0.0001†§
	Delayed recall (max = 10)	6.7 (1.7)	1.6 (1.5)	0.7 (1.3)	<0.0001†§
	Recognition (max = 10)	9.7 (0.5)	7.5 (1.5)	7.0 (1.6)	<0.0001†§

† significant difference between controls and minimal DAT subgroup

§ significant difference between controls and mild DAT subgroup

¥ significant difference between minimal and mild DAT subgroups

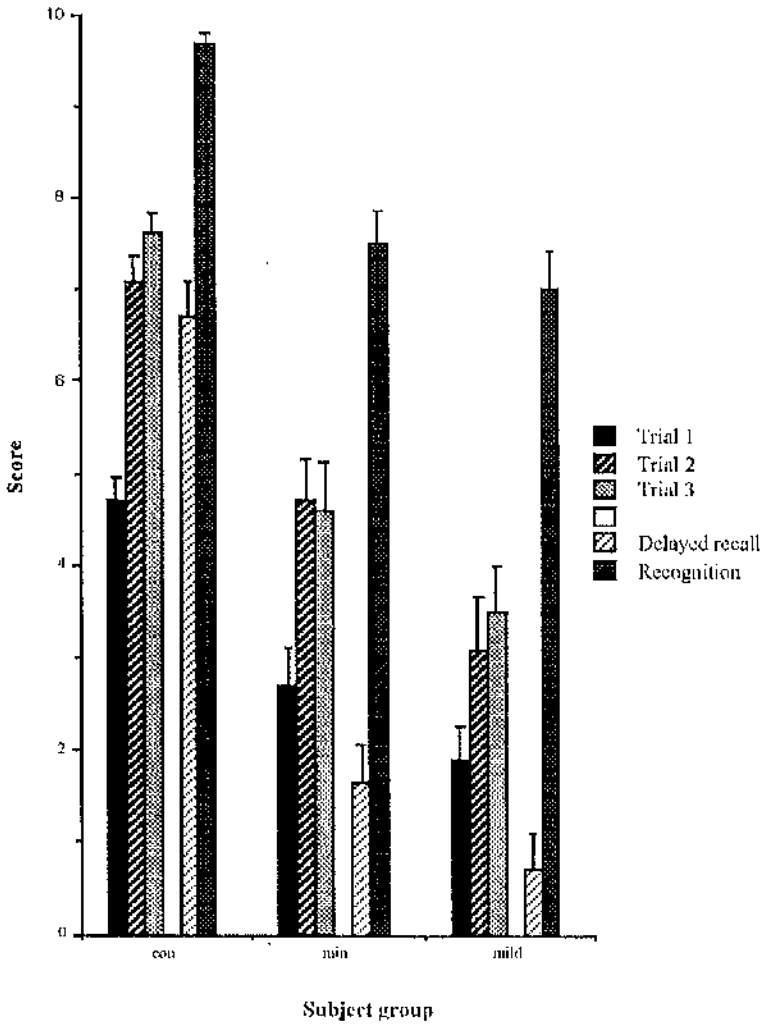
NS difference non-significant

Figure 6.1 illustrates the rate of learning over the 3 trials, as well as delayed recall in the controls and patient groups. It can be seen that by trial 3, the normal controls had learned a mean of 7.6 of the ten items and after a short delay were still able to recall 6.7 items. Both DAT groups, by contrast, showed substantial impairments in all conditions.

A 3 (group) x 3 (trials) ANOVA with repeated measures revealed significant main effects of group ($F(2,60)=37.2$, $p<0.0001$) and condition ($F(2,120)=74.3$, $p<0.0001$), and a significant interaction ($F(4,120)=3.4$, $p<0.01$). Post-hoc one-way

ANOVAs across trials showed that both controls and minimal DAT patients showed significant learning across trials ($F(2, 58)=37.0$, $p<0.0001$ and $F(2,32)=5.5$, $p<0.01$ respectively), but this was not evident in the mild group ($F(2,30)=3.0$, $p>0.05$), indicating that mild DAT patients obtained little benefit from repeated attempts at learning.

Figure 6.1. Performance for three trials of immediate recall, delayed recall and recognition on CERAD word list by controls, and minimal and mild DAT patients, with standard errors



For delayed recall there was a highly significant group effect ($F(2,60)=93.6$, $p<0.0001$). Post hoc analysis showed that, although both patient groups were impaired with respect to controls ($p<0.0001$), there was no difference between patient groups ($p>0.05$).

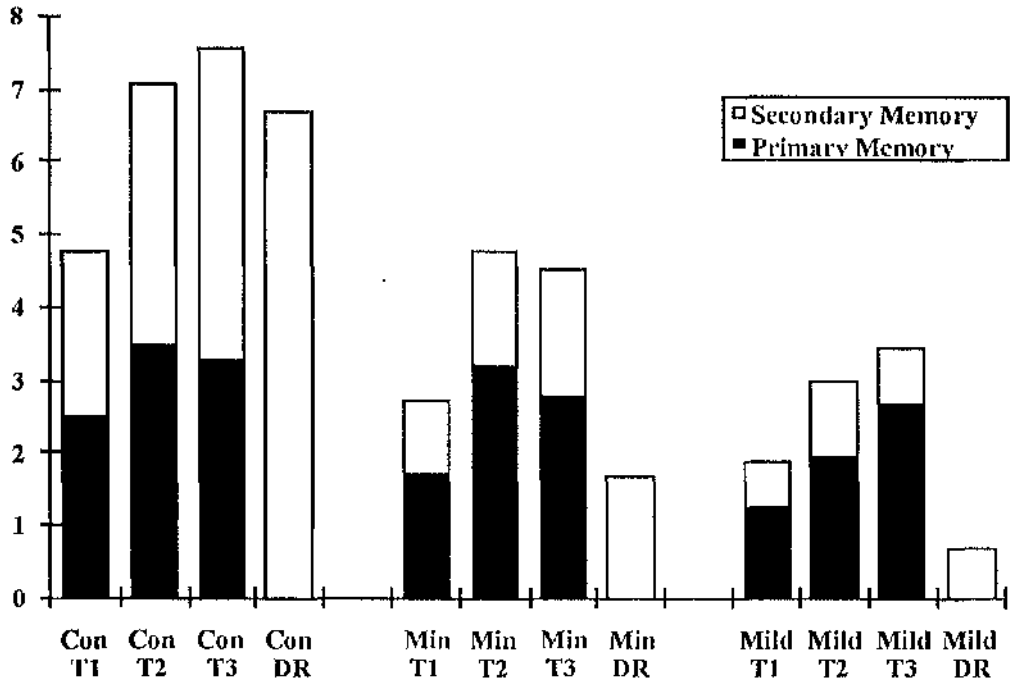
Comment

At first sight, the CERAD word list test appears to show a relatively straightforward pattern of impaired performance in the DAT groups, coupled with greater forgetting. However, it is important to bear in mind that the three learning trials are each followed by immediate free recall, and as such are likely to comprise two rather different components, a durable long-term or secondary memory component, and a more labile short-term or primary memory component that is principally reflected in the presence of a recency effect in immediate, but not delayed free recall. There is evidence to suggest that these two components are differentially affected by DAT, with the secondary memory component being seriously impaired, while primary memory is relatively spared [305]. Fortunately, a number of methods exist which allow the two to be separated. While all these methods make certain theoretical assumptions, perhaps the most pragmatic is that proposed by Tulving and Colotla [332], which defines the primary memory items as those recalled with seven or less items interpolated between presentation and recall. For example, if an input sequence consisted of items A B C D and E and the subject recalls E C D and A, the interpolation scores would be 0, 3, 3 and 8 respectively; hence items E C and D would be regarded as recency items, but A would not. Note that this measure assumes that an item is in either primary or secondary memory, but ignores the case of items which may be simultaneously registered in both. I shall return to this assumption after discussing the data.

The contribution of primary and secondary memory - Tulving and Colotla's method

Figure 6.2 shows the learning and delayed recall scores for the CERAD word learning task, split into primary (PM) and secondary memory (SM) components. In the case of primary memory, a repeated measures ANOVA indicated significant main group ($F[2,60]=9.0$, $p<0.0005$) and trial effects ($F[2,120]=22.2$, $p<0.0001$), but no group by trial interaction ($F[4,120]=2.1$, $p>0.05$).

Figure 6.2. Performance for three trials of immediate recall (T1, T2, T3) and delayed recall on CERAD word list by controls, and minimal and mild DAT patients, with standard errors. Performance on immediate recall is expressed in terms of contribution of working and long-term memory



This result is consistent with the report by Wilson *et al* [357] of a small deficit in DAT patients of PM, as measured using the Tulving and Colotla method, but is at odds with the observation by Spinnler *et al* [305] of relatively preserved PM in DAT patients, as reflected by the recency effect. There is, in addition, a suggestion that DAT patients may improve the contribution of working memory across trials, although this did not reach statistical significance. By contrast, the SM component showed significant group ($F[2,60]=31.4$, $p<0.0001$) and trial effects ($F[2,120]=16.0$, $p<0.0001$), and a group by trial interaction ($F[4,120]=3.67$, $P<0.01$). Post hoc analysis indicated that this was due to controls improving with repeated trials ($p<0.0001$), while DAT patients obtained no significant benefit from repeated trials on the SM component of performance ($p>0.05$). The learning pattern appears to be relatively straightforward, with an approximately equivalent PM component for all groups, coupled with a SM component that is significantly larger in the control group and shows enhancement over trials, in contrast to the two patient groups who show a smaller and static SM component.

In the case of delayed recall, the recency effect is of course obliterated by the intervening activity, leaving only the SM component. If one makes the simplifying assumption that all items are either in PM or SM, then loss of information from secondary or long term memory can be measured by comparing the SM component on trial three with delayed recall. A repeated measures ANOVA indicated significant group ($F[2,60]=3.14$, $p<0.001$) and trial effects ($F[2,120]=16.0$, $p<0.001$), and a group by trial interaction ($F[4,120]=3.67$, $p<0.01$). Post hoc analysis indicated that this was due to the fact that the SM contribution to trial three was significantly less than to delayed recall in controls ($p<0.001$), while DAT patients showed no such difference ($p>0.05$).

Data from the DAT patients can be explained relatively easily on the assumption that over the brief intervening delay, the only loss was of items that were registered in PM. Such an assumption is clearly not applicable to the performance of the control subjects, since it would imply that the number of items in SM had dramatically increased over the delay. A much more plausible interpretation is to assume that the Tulving and Colotla estimate of PM is inappropriate in this case.

As mentioned earlier, the Tulving and Colotla measure is a pragmatic one based on the simplifying assumption that PM can hold about seven items, and hence that all items that are recalled with fewer than seven interpolated items can be assumed to be held within that system. There are a number of reasons for questioning this approach. First of all, "the magic number seven" has been applied principally to digit span [222], which relies on a very different mechanism from the recency effect in free recall [18]. A second problem lies in the assumption that an item resides either in PM or in SM, with no items being registered in both. This is a questionable assumption when applied to single trial free recall, but is clearly incorrect when multi-trial recall is involved. Consider as an extreme case, the position when a subject has learned the whole list. By definition all items would then be in SM. It is quite likely, however, that some items would be recalled following fewer than seven interpolated items, and hence accordingly to the Tulving and Colotla formula should be regarded as in PM, and not in SM. It could, of course, be argued that the Tulving and Colotla formula was designed for single trial immediate free recall, and hence despite the fact that it appears to make sense of the performance of the DAT patients, that its use is not justified.

The contribution of primary and secondary memory - Waugh and Norman, and Raymond's method

Fortunately, however, there is a second method of assessing PM that uses different assumptions, which allow for items to be registered in PM, SM or both. The method is based on analysis of the serial position curve and was developed from the work of Waugh and Norman [345] by Raymond [265]. The SM component is estimated on the basis of the flat middle portion of the serial position curve, which is assumed to have little or no PM involvement. In contrast, the recency effect is assumed to be principally based on PM, but can be corrected using the assumption that some of the recency items would also be stored in SM. While a marked recency effect would be expected for single trial immediate free recall, it is far from clear that PM will play an equivalent role in multi-trial recall as used in the CERAD test. To address this experimental/theoretical approach, I collapsed the two DAT groups into one to give me sufficient data points to draw meaningful serial position curves. Whereas previously I was using the data to address clinical/psychometric concerns, in which the stage of DAT is important, here I am trying to establish whether there is a difference in strategy between the DAT patients and controls.

I began, therefore, by plotting serial position curves for the controls and combined DAT groups for each of the three trials. Figure 6.3 shows the resulting performance pattern for the control subjects. While there is a suggestion of a recency component for trials one and two, the serial position curve is far from typical of immediate free recall, while the third trial shows a virtually flat function with little or no recency.

Figure 6.3. Effect of order of presentation on proportion of items recalled by control subjects on CERAD immediate recall

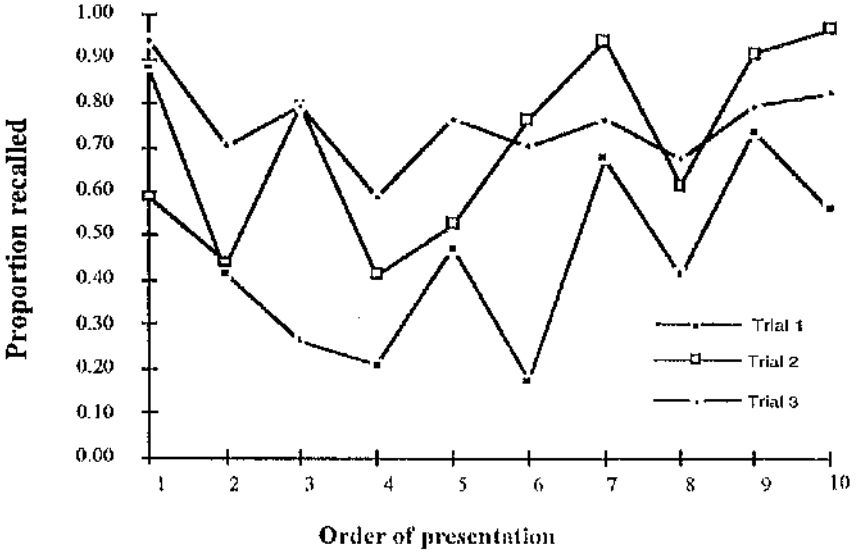
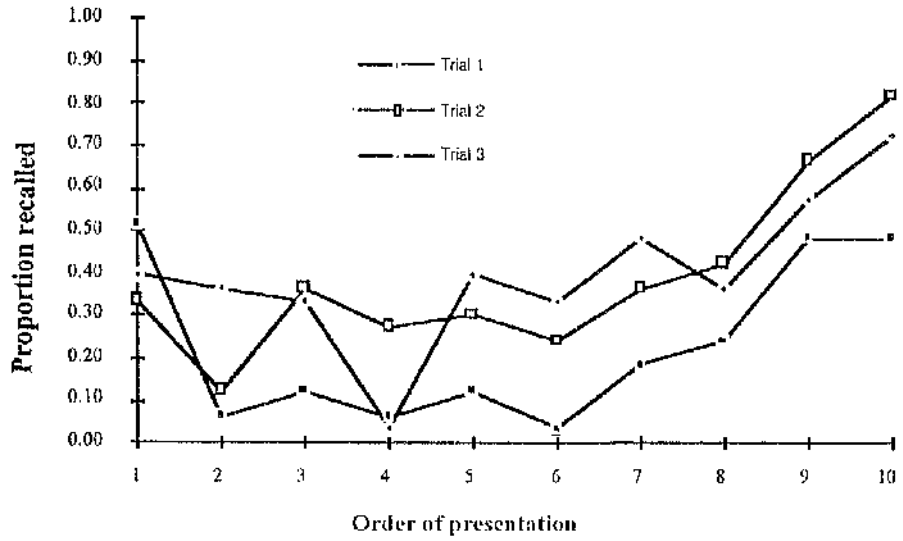


Figure 6.4. Effect of order of presentation on proportion of items recalled by DAT patients on CERAD immediate recall



In contrast, as Figure 6.4 shows, the DAT patients showed marked evidence of recency on all three trials, suggesting a continued reliance on the PM component of memory. In calculating the PM and SM components, item one was discarded, since it was clear that some subjects continued to rehearse this item throughout the list, making it effectively a PM item. SM was computed on the basis of performance on items two to six, while the recency effect was calculated on the basis of performance over the last four items. Ideally, the recency effect should be corrected for the contribution of PM to the relevant items. Unfortunately, however, this presented problems in the case of my data, both from ceiling effects in the control group (resulting from the use of a relatively short list and three learning trials) and the floor effects in the case of some of the DAT subjects. The nature of the correction formula makes ceiling and floor effects particularly disruptive, and for that reason I chose to use a simple uncorrected measure of recency based on performance over the last four items.

I then performed a group (AD or control), by memory component (secondary memory or recency), by trial MANOVA. The results indicated that there was a group effect [$F(1,61)=40.0$, $p<0.0001$)], a memory component effect [$F(1,61)=11.6$, $p<0.0001$)] and a trial effect [$F(2,122)=71.0$, $p<0.0001$)]. There was also a group by memory component by trial three-way interaction [$F(2,122)=3.17$, $p<0.05$)].

Subsequent repeated measures ANOVA for primary memory indicated a group effect [$F(1,61)=13.1$, $p<0.001$)], a trial effect [$F(2,122)=21.4$, $p<0.0001$)] but no group by trial interaction [$F(2,122)=0.4$, $p>0.05$)]. By contrast, for secondary memory, repeated measures ANOVA showed a group effect [$F(1,61)=61.8$, $p<0.001$)], a trial effect [$F(2,122)=19.0$, $p<0.0001$)] and a group by trial interaction [$F(2,122)=7.2$, $p<0.001$)]. This was due to controls showing a significant improvement of secondary memory over trials [$F(2,58)=16.7$, $p<0.001$)], while DAT patients showed no such improvement [$F(2,64)=2.7$, $p>0.05$)].

Although primary memory is mildly impaired in DAT with respect to controls, both controls and DAT patients show a similar improvement across trials. This contrasts with the pattern seen in secondary memory. Here, controls show benefit with repeated trials. DAT patients show no such improvement in secondary memory across trials. I can conclude from this analysis that there is relative sparing of primary memory in DAT, but that secondary memory is significantly impaired. Also, in controls, repeated trials improve secondary memory performance. By contrast, repeated trials do not improve secondary memory performance in DAT patients, i.e. they approach each of the three trials as if in a single trial free recall paradigm.

This suggests that the two groups tackle the CERAD learning task in a somewhat different way. This is also supported by the serial position curves. The

control subjects begin by showing a tendency to recency, although the serial position curve is far from classic, but by trial three have apparently abandoned a recency strategy. In contrast, the DAT patients continued to respond as if in a single trial free recall paradigm.

As Table 6.2 indicates, there was a highly significant effect of group on recognition performance ($F[2,60]=34.5$, $p<0.0001$), with the patient groups being significantly impaired relative to control subjects ($p<0.0001$), but with no significant difference between the two patient groups ($p>0.05$). While this clearly reinforces the conclusion of impaired learning in the two DAT groups, the data do not allow a direct comparison of recall with recognition since the two scores are not standardised. Furthermore, interpretation is constrained by the fact that performance in the control subjects is virtually at ceiling.

Doors and People Test

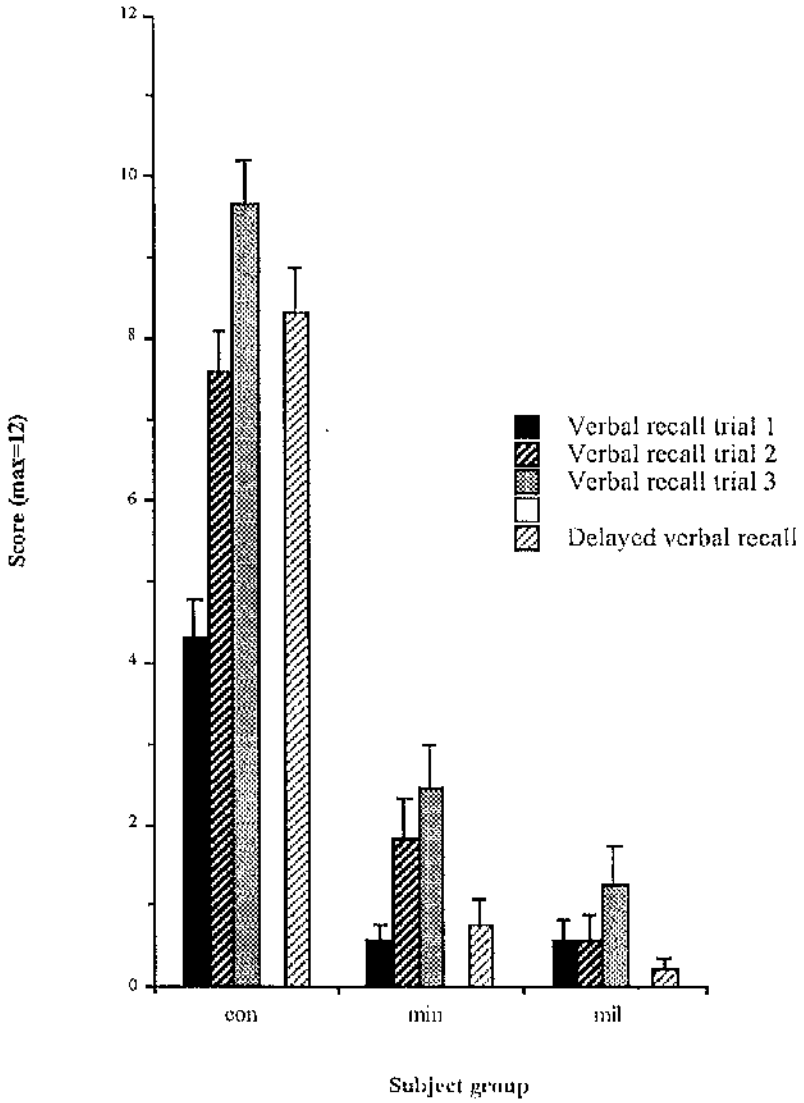
Performance on this test is shown in Table 6.3. Analysis of the overall score showed a significant group effect ($F[2,60]=56.3, p<0.0001$), with control subjects performing at a significantly higher level than the minimal or mild groups [con vs. min ($p<0.0001$), con vs. mild ($p<0.0001$)], which do not differ significantly ($p>0.05$). Essentially the same pattern obtains for each of the four subtests, with an overall group effect ($p<0.0001$) in each case, represented principally by a difference between controls and DAT patients ($p<0.0001$ in each case), and a tendency for the mild DAT patients to perform more poorly than the minimal which reaches significance only for one of the four conditions, namely nonverbal recall ($p<0.05$).

Table 6.3. Performance of controls, minimal and mild DAT patients on the Doors and People Test.

		Controls	Minimal DAT	Mild DAT	p-values
		n=30	n=17	n=16	
Doors & People Test					
Overall Score		9.2 (3.4)	2.9 (2.3)	1.1 (1.4)	<0.0001†§
Verbal	Recall	8.9 (2.9)	4.3 (1.4)	3.9 (0.7)	<0.0001†§
	Recognition	9.7 (3.4)	5.8 (3.0)	4.2 (2.6)	<0.0001†§
Nonverbal	Recall	10.1 (4.5)	5.4 (2.7)	2.8 (1.6)	<0.0001†§¥
	Recognition	9.1 (3.4)	5.6 (1.4)	4.2 (1.4)	<0.0001†§
Forgetting	Verbal	10.2 (3.7)	10.2 (2.9)	11.1 (2.1)	NS
	Nonverbal	10.9 (3.4)	9.2 (4.5)	8.9 (3.6)	NS
Total forgetting		11.0 (3.2)	9.8 (3.9)	10.1 (2.7)	NS
Visual-verbal discrepancy		10.2 (2.2)	10.5 (1.3)	10.2 (0.7)	NS
Recall-recognition discrepancy		10.1 (2.7)	9.6 (1.5)	9.3 (1.0)	NS

A more detailed analysis of the processes of learning and forgetting can be obtained from the subtests involving learning to recall the shapes and the names of four people. The results of these two tests are shown in Figures 6.5 and 6.6, respectively. Considering first the name learning task, a three (groups) by three (conditions) ANOVA with repeated measures showed significant main effects of group ($F[2,60]=65.0$, $p<0.0001$) and condition ($F[2,120]=30.5$, $p<0.0001$), together with a significant interaction ($F[4,120]=12.2$, $p<0.0001$). Post hoc analysis confirmed that controls were superior to both patient groups ($p<0.0001$), but that there was no difference between the two patient groups ($p>0.05$). The group by condition interaction indicated that the groups differ in their learning rate. The controls showed significant improvements between trials 1 and 2 ($p<0.0001$), and between trials 2 and 3 ($p<0.0005$). The minimal DAT group showed significantly better performance on trial 2 than on trial 1 ($p<0.05$), but no further enhancement between trials 2 and 3 ($p>0.05$), while the mild DAT patients showed no difference between any of the three trials ($p>0.05$). In short, while the control subjects showed steady improvement, the DAT patients showed little or no progressive learning.

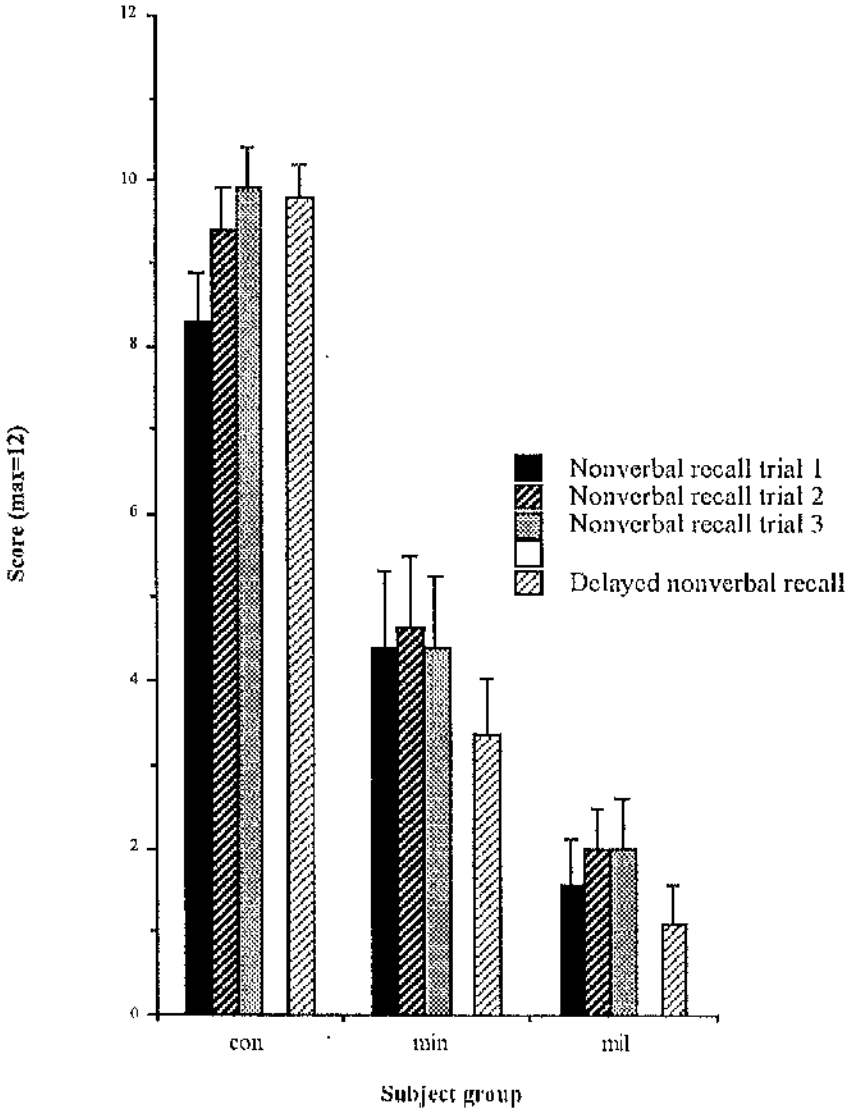
Figure 6.5. Performance for three trials of immediate verbal recall, delayed recall and recognition on the Doors and People Test by controls, and minimal and mild DAT patients, with standard errors



A similar analysis of the shapes test again indicated a significant main effect of group ($F[2,60]=43.3$, $p<0.0001$), an effect of trial ($F[2,120]=5.8$, $p<0.0005$), but no significant interaction ($F[4,120]=1.73$, $p=0.15$). Although the interaction between group and trial failed to reach significance, inspection of Figure 6.6 suggests that the significant trials effect is attributable almost entirely to the control subjects, a conclusion that is supported by the presence of the significant trials effect in the control group ($F[2,58]=8.8$, $p<0.001$), and its absence in either the minimal or mild DAT groups [($F[2,32]=0.15$, $p>0.05$) for minimal, ($F[2,30]=0.44$, $p>0.05$) for mild].

Hence, although the amount of learning across trials is less marked for this task, the overall pattern of results resembles that for the name learning subtest, with controls showing a substantially higher level of performance, together with accumulation of learning over trials, in contrast to the poorer performance and lack of cumulation of learning in the DAT patients.

Figure 6.6. Performance for three trials of immediate nonverbal recall, delayed recall and recognition on the Doors and People Test by controls, and minimal and mild DAT patients, with standard errors



Forgetting

The test procedure for the verbal learning task was explicitly designed to avoid immediate recall of the most recently presented item, hence eliminating complication by a primary memory component. Consequently the difference between trial 3 performance and delayed recall can be used as a relatively straightforward measure of loss of information from long term memory. Unfortunately, for visual recall, the subject is allowed to reproduce the crosses in any order. If the subject first draws the cross last presented, then primary memory may be contributing to immediate recall. This could have been circumvented by asking the subject to reproduce the crosses in the correct order, but this introduces spatial memory, given that the subject had initially copied the crosses. For this reason, my conclusions regarding the forgetting rate are most robust for verbal recall. Scaled forgetting scores were calculated and are shown in Table 6.2, from which it is clear that overall amount of forgetting was within the normal range, and did not differ between groups, whether considered overall ($F[2,60]=0.89$, $p>0.05$), or split into separate functions for verbal and nonverbal tasks [($F[2,60]=0.42$, $p>0.05$) for verbal, ($F[2,60]=1.83$, $p>0.05$) for nonverbal]. This pattern of results is consistent in suggesting that once material has been learnt, then DAT patients do not show differential loss of information from secondary or long-term memory.

Recall-recognition

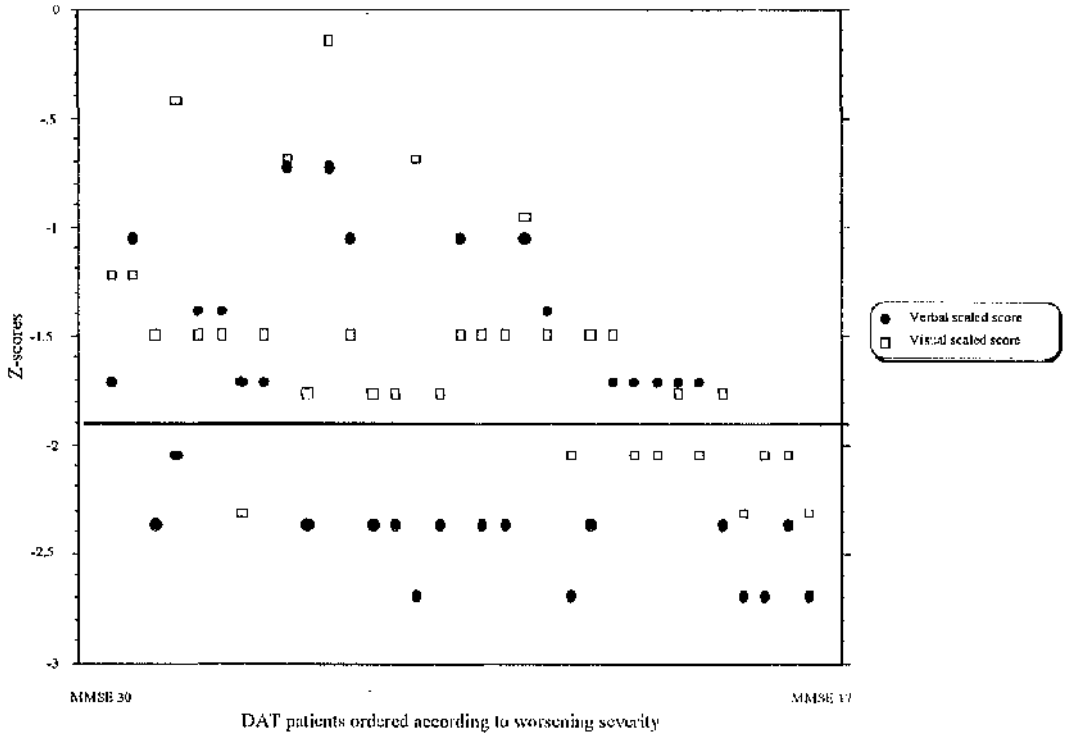
A second question concerns the role of retrieval in the impaired memory performance of the DAT patients. If retrieval is a major component of the deficit, then one might expect the effect of conditions to be more marked when measured by recall than when based on recognition scores. The presence of standardised scaled scores allows a direct comparison of recall and recognition to be made, and to be reflected directly in the scaled recall-recognition discrepancy scores. As Table 6.2 indicates, both recall and both recognition measures show very substantial effects of condition. The scaled recall-recognition discrepancy scores confirm the impression that recall and recognition scores are approximately equivalent, with scaled scores of 10.1, 9.6 and 9.3 for the control, minimal and mild groups respectively, (absolute equivalence would be reflected by a scaled score of 10). There was no suggestion of a difference between these three scores ($F[2,60]=0.77$, $p>0.05$), generally supporting the view that the DAT deficit is one of learning rather than of retrieval. That does not of course imply that retrieval processes are necessarily normal in DAT patients, but it does suggest that the limit on performance by DAT patients on this test is set by failure to learn, rather than difficulty in retrieving what has been learned.

Material-specificity

A final question concerns the issue of material-specificity. This could be reflected either by a general visual-verbal discrepancy, indicating that DAT has a greater impact on one type of learning, or alternatively, it might vary from one individual to another, with some subjects showing a particularly marked tendency for verbal memory impairment, while other subjects might show the opposite, possibly reflecting the differential spread or cortical distribution of the disease [15]. The overall scaled visual verbal discrepancy score is shown in Table 6.2. All three groups give scores that are very close to the scaled score of 10 indicating equal deficits for visual and verbal memory, with no suggestion of an effect of group ($F[2,60]=0.22$, $p>0.05$). Such an overall picture could, however, be consistent with the presence of a substantial degree of material-specificity across individuals, provided that subjects were approximately equally likely to show visual or verbal deficits.

Figure 6.7 shows the relevant visual and verbal scaled scores for each of the DAT subjects, plotted as a function of severity as measured by MMSE performance. While there is a clear general impairment in performance, this tends to characterise both visual and verbal memory. There is a suggestion that verbal memory may be slightly more sensitive, with 21 subjects showing poorer verbal than visual performance, while 10 showed the reverse, but for most subjects the difference is rather small, with no subject showing a difference between the two scale scores that is greater than two standard deviations. The pattern therefore appears to be one of general memory deficit, with some individual variability, but with little evidence of the marked material-specificity seen in patients who have undergone left versus right temporal lobectomy [235].

Figure 6.7. Univariate scattergram of Z-scores of verbal and nonverbal memory scores, plotted in order of increasing dementia severity, with line drawn at 95% confidence interval for controls



Discussion

I set out to study the episodic learning and memory deficit in DAT patients using three measures, immediate and delayed verbal recall, the CERAD word learning test, and the Doors and People test. All three show a very marked impairment in performance in both DAT groups, while showing relatively poor capacity to distinguish between the mild and minimal patient groups. All three are, therefore, sensitive to the effects of DAT, but are probably not ideal for monitoring the stages of the disease.

A second question concerns the effect of DAT on the cumulative acquisition of material. The logical memory test is not appropriate for investigating this aspect of learning, but both CERAD word list learning, and the shapes and people learning subtests of the Doors and People Test indicate that learning is cumulative across trials in control subjects. In the case of the DAT patients however, there is little evidence of cumulation on either the secondary memory component of the word list test, or on the shapes and people learning tests. Delayed recall in each case indicates that some

learning has taken place, suggesting that the problem is not simply one of the absence of any long term or secondary memory component. The most likely interpretation of this pattern of results might be to assume that cumulative learning demands an active organisational strategy, whereby groups of items are integrated into progressively larger chunks [331].

The pattern of results for forgetting across the three tests is somewhat more complex due to the problem of separating out the contributions of primary and secondary memory to immediate recall in the prose and word list conditions. I know of no way of separating out the contribution of working memory to immediate prose recall, but suspect that it can in certain cases be substantial, as for example with highly intelligent but densely amnesic patients who may perform above average on immediate recall, while showing no recall after a brief delay [357]. For that reason, while the immediate and delayed recall of prose may be a measure of considerable practical usefulness, its theoretical interpretation remains problematic.

In the case of the CERAD word list learning test, methods for separating out the primary and secondary memory components are available. Two ways of correcting for primary memory were explored. The Tulving and Colotla method, which relies on number of items intervening between presentation and test, gave results that appeared to be plausible for the DAT patients, but was less satisfactory for control subjects due to the assumption that an item is stored in either primary memory or secondary memory, but not in both. The alternative measure which utilises the shape of the serial position curve makes the assumption that items may be registered in both systems, and gives a more satisfactory account of the data for control subjects who demonstrate cumulative learning across successive trials. In general, the most satisfactory account of the nature of forgetting in my subjects would seem to be that whereas the amount of information lost over a delay is greater for DAT patients, this is likely to be the result of their greater reliance on primary memory, rather than reflecting a more rapid loss of information from long-term memory.

The role of retrieval in the DAT deficit can be addressed by a direct comparison of recall and recognition measures. While the CERAD word list might appear to offer this option, interpretation of any differences between recall and recognition are constrained by the presence of a ceiling effect in the recognition score for the control subjects, and by problems in the comparability of the two measures, making them unsuitable for direct use to generate a recall-recognition index.

The standardisation of recall and recognition measures in the Doors and People test does allow the computation of a recall-recognition index. This index provides no evidence that the patients are substantially more impaired on recall than recognition,

suggesting that the deficit is principally one of learning, rather than one of retrieving what has been learned. That does not, of course, mean that retrieval processes are necessarily well preserved in DAT patients, merely that in the absence of adequate learning, retrieval limitations are of limited significance.

Finally, the Doors and People Test allows for the investigation of material-specificity in my sample of DAT patients. In contrast to the results of Becker *et al* [29], I find little evidence for marked material-specificity in my subjects. However, Becker *et al* used immediate and delayed prose recall as their measure of verbal memory. As we saw earlier, immediate recall may have a substantial working memory component, while delayed recall tends to show a floor effect. Their measure of visual memory, the Rey-Osterreith figure, is a very different task that may have a substantially less pronounced working memory and semantic coding component than occurs in prose recall. In general, it seems desirable that conclusions about material-specificity should attempt to use tasks that are as comparable as possible other than on the material-specific dimension. Where possible, each dimension should be assessed using two separate measures, or at least a replication of the original measures, so as to avoid confounding possible test unreliability with material-specificity. My more detailed analysis of individual subjects suggests that individuals do differ in the relative magnitude of visual or verbal impairment, but that this represents variability within a broad general tendency for both verbal and visual memory to decline.

I split my DAT group into two subgroups in the hope of investigating the extent to which the various measures would prove useful in monitoring the stages of the disease. If, as seems reasonable, I assume that a lower MMSE score represents a later stage of the disease, then one might expect a satisfactory staging measure to distinguish between the two groups of patients. Virtually the only measure to separate these two groups was immediate prose recall. Taken at face value, this then is the only satisfactory measure for staging the progress of the disease from the range of tests used.

Before drawing this conclusion, I should, however, consider another possibility. Although there are correlations between MMSE score and neuropathological changes [324], my assumption that MMSE score represents the stage of the disease may be an over-simplification. Performance on MMSE presumably reflects the overall cognitive performance of the patient, which in turn may depend both on the premorbid abilities of the patient and on the progress of the disease. If one assumes that the memory deficit is less dependent upon premorbid level than is MMSE performance, then memory tests might be a better marker of the stage of the disease than the MMSE. On the other hand, unlike memory tests, the

MMSE assesses many aspects of cognition. As dementia progresses, most aspects of cognition area affected and the MMSE will, therefore, be superior to memory tests for staging DAT. Thus, both memory tests and the MMSE have their own advantages as measures of disease severity.

It is clearly the case that performance of both groups of patients is low on virtually all the memory measures, with the possible exception of immediate prose recall. This raises the problem of using norms based on the general population in order to obtain standardised scores. This is clearly a problem for any test using the standard procedure of expressing patients' performance in terms of the normal population. I am not advocating the abandonment of this very useful method of comparison, but simply draw attention to the fact that the further a patient drops below the normal range of performance, the greater the caution that should be employed in interpreting scaled scores. Indeed, if one hopes to monitor the later stages of cognitive decline in DAT patients using memory measures, further easier tests will need to be developed. It seems likely that normal subjects will perform perfectly on such tests, making conventional standardisation in terms of the general population inappropriate. This makes it necessary, however, to use standardised measures on patients at an early stage of the disease if one aims to provide an adequate theoretical analysis of the nature of the episodic memory deficit. Using this method my data suggest that the impaired episodic memory of DAT patients reflects a failure to learn, rather than faster forgetting or impaired retrieval.

Summary

Anterograde episodic memory was assessed in a cohort of 33 patients with early dementia of Alzheimer type (DAT) and 30 matched controls using immediate and delayed prose recall, the CERAD word learning test, and the recently developed Doors and People Test of visual and verbal recall and recognition. DAT patients showed markedly impaired learning on all three measures, with little evidence of cumulation of information across trials. Patients showed more forgetting than controls on prose recall and the CERAD word list, but more detailed analysis suggested that this differential loss was attributable to the contribution of primary memory to immediate but not delayed recall. No differences in forgetting rate were observed on the Doors and People test. Scaled scores were used to derive a recall-recognition index, together with a measure of material-specific memory based on the ratio of verbal to visual memory deficits. There was no evidence for differential sensitivity of recall over recognition, implying that the episodic memory deficit is one of learning, rather

than of the retrieval of learned material. Although individuals varied in the relative degree of impairment of verbal and visual memory, there was no general tendency for material-specificity. It was concluded that the episodic memory deficit in DAT is general in nature and primarily reflects impaired learning rather than accelerated forgetting or disrupted retrieval.

Chapter Seven

Neuropsychology of memory and SPECT in the diagnosis and staging of dementia of Alzheimer type

Introduction

As outlined in the Introduction, there is currently controversy over the relative benefits of neuropsychology and functional imaging as aids to the diagnosis and staging of DAT. This section of the thesis addresses the controversy.

Neuropsychology in diagnosis and staging DAT

The use of neuropsychological methods in diagnosis and staging of DAT has been extensively studied. Since the first aspect of cognition to be affected by DAT pathology is almost invariably memory, neuropsychological tests which try to differentiate between patients with the earliest manifestations of the disease and controls usually focus on memory, in particular those which test delayed recall of newly acquired information [88]. For instance, Huppert and Beardsall [158] found that recall of object name and name recall from the Rivermead Behavioural Memory Test were the best memory tests for discriminating between DAT patients and elderly controls. Likewise, Storandt *et al* [316] found that a battery of tests comprising the logical memory and mental control subtests of the Wechsler Memory Scale, Form A of the Trailmaking Test, and word fluency for letters S and P could classify successfully 98% of patients with mild DAT and matched controls. Mohs *et al* [224] found recall of use in diagnosis, whereas recognition was of use in staging.

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has analysed diagnosis and staging DAT in detail using a battery of neuropsychological tests comprising the MMSE, naming, verbal fluency, praxis and memory; delayed recall was found to be the best discriminator between controls and DAT patients [352]. In a follow-up study, delayed recall and naming were confirmed as the best discriminators [353] while recognition memory, verbal fluency and praxis were of use in staging DAT; delayed recall was of no use in staging because of "floor effects" early in the illness.

Functional imaging in diagnosis and staging DAT, and the anatomical distribution of DAT pathology

Having explored in earlier sections of the thesis the nature of the episodic, remote and working memory deficits in DAT, this chapter is concerned more with the practical issue of the value of neuropsychological tests of memory in the diagnosis and staging of DAT. Comparative studies of CT, MRI and PET (positron emission tomography) conclude that functional imaging is the most sensitive imaging modality for the diagnosis of DAT [106]. For instance, Herholtz *et al* [138] estimated that PET was 92% sensitive and 80% specific for DAT.

Positron emission tomography

With regard to the localisation of initial PET changes in DAT, most investigations have shown temporoparietal hypometabolism early in the course of the disease,

followed by frontal changes later [254]. Moreover, Frackowiak *et al* [110] found that temporoparietal metabolism correlated with dementia severity. The proportion of cases showing this "classical pattern" may have been exaggerated; a recent study demonstrated bilateral temporoparietal hypometabolism in only 38% of DAT patients [260]. Similarly, Kumar *et al* [194], using high-resolution PET, found that regional cerebral metabolic rates for glucose in most major neocortical and subcortical grey matter regions, and certain metabolic ratios, discriminated even mildly demented patients from controls, with the severest metabolic abnormalities occurring in the association cortices.

Welsh *et al* [354] studied whether PET conferred any additional benefit over neuropsychology in the early detection and discrimination of DAT from other brain disorders. Discriminant analysis showed that the addition of PET data to neuropsychological data did not significantly improve discrimination between DAT and other memory disorders. They conclude that PET may provide some additional information to the clinical evaluation of dementia, but should be considered confirmatory and not diagnostic of DAT. Similarly, Haxby *et al* noted that some of their mildly demented DAT patients had normal PET scans [133]. But importantly, they also found that metabolic defects on functional imaging may precede neocortically-mediated cognitive deficits, (e.g. aphasia, visuo-spatial impairment). It may be that neuropsychological tests are able to detect mnemonic dysfunction prior to functional imaging showing any hypometabolism Once established, however, further spread of pathology to temporoparietal association areas may be detected by PET imaging, prior to the detection of language and visuo-spatial dysfunction.

Although PET scanning may be the definitive functional imaging technique, it has limited applications in clinical practice due to its extreme cost and restricted availability. This has led to the development of cheaper and more widely available nuclear medicine scanning techniques. SPECT (single photon emission computed tomography) can produce images of sufficient quality to be used in studies relating regional cerebral blood flow to neuropsychological function. It is therefore pertinent to examine the role of SPECT as a discriminative and staging tool in DAT.

Single photon emission computed tomography

The majority of investigators have found changes on SPECT similar to those found with PET, i.e. characterised primarily by bilateral reduction of rCBF in the posterior temporoparietal cortex [51, 77, 157, 167, 241]. Hanyu *et al* [129] found that temporoparietal hypoperfusion was 82% sensitive and 89% specific for the diagnosis of DAT; although this pattern of hypoperfusion was present even in patients with mild DAT, it should be noted that 18% of their patients did not show this. Very similar rates of diagnostic accuracy were found by Johnson *et al* [170]. A number of research groups have reported that temporoparietal hypometabolism correlates strongly with dementia severity as measured by MMSE [164, 218]. In a prospective

study of patients with cognitive dysfunction, Holman *et al* [152] found that bilateral posterior cortical rCBF (regional cerebral blood flow) defects indicated a high probability of the presence of DAT, although this pattern occurred in only 27% of DAT patients. Unilateral posterior rCBF and frontal rCBF defects were not predictive of DAT.

More recently, however, Waldemar *et al* [340] did not find the above predicted pattern of progression. They found that global CBF was reduced in DAT, but that there was no disproportionate reduction of rCBF in any brain region, and suggested that the heterogeneous patterns of rCBF deficits may reflect different stages of the disease or cognitive subtypes. Partial support for this was provided by Cappa *et al* [61] who studied the use of SPECT in the detection of the early onset of DAT, and found not only posterior temporoparietal, but also frontal perfusion, to be of most use in discriminating DAT patients from controls.

Combined studies of neuropsychology and SPECT have tended to address the anatomical localisation of cognitive function [117, 230, 246] rather than directly comparing the use of neuropsychology and SPECT for diagnosis and staging. As with the PET studies discussed above, there is some evidence that SPECT scanning may be normal in patients with early DAT when neuropsychological memory tests are clearly abnormal [266]. This aspect has not been fully addressed and there is a need for further investigations of patients with early stage disease, especially as it is these cases which present diagnostic difficulty.

Aims

I wished to answer the following questions:

1. How sensitive are neuropsychological measures of memory ability in diagnosing and staging DAT ?
2. How sensitive is SPECT in diagnosing and staging DAT ?
3. Do my SPECT data support the accepted pattern of spread of DAT pathology, i.e. initially temporo-parietal with subsequent frontal involvement, or is the pattern more heterogeneous ?
4. Are there cases of DAT diagnosed clinically who have abnormalities on neuropsychological testing but who have normal SPECT scans ?

Experiment 1 - Neuropsychology

Methods

Subjects

Two groups consisting of a total of 63 subjects participated in the study: 33 patients with DAT (21 females and 12 males) and 30 neurologically-intact normal control subjects (16 females and 14 males). These are the same subjects as described in the previous Chapters. Further details are provided in Chapter 2. Written informed consent was obtained from all subjects or the caregivers, where appropriate.

Neuropsychological tests of memory

A range of tests designed to assess various aspects of explicit memory were administered. These tests are listed in Table 7.1 and are further detailed in the Chapter 2.

Statistical analysis

To determine the use of neuropsychology in discriminating DAT patients from controls, I applied unpaired comparisons using Student's t-test [1]. Because of the number of comparisons performed, only differences with a p-value of <0.01 were accepted as significant. To assess the maximum prediction of group membership with the minimum number of variables significantly contributing to that group separation, stepwise logistic regression with backward elimination was employed [306].

To assess the role of neuropsychology in staging DAT severity, stepwise linear regression analysis was undertaken. The independent variables (neuropsychological tests) were used to determine dementia severity as measured by MMSE, and each independent variable was entered one by one, in decreasing order of importance, to predict the dependent variable, in this case MMSE.

Results

Table 7.1 gives the neuropsychological test data. It can be seen that all neuropsychological tests with the exception of the dual performance components of the Test of Everyday Attention and Della Sala *et al*'s test, recognition of famous faces and NART IQ, revealed significant ($p<0.01$) differences between DAT patients and controls. These data are the same as those shown in Chapters 3, 5, and 6 where the results are discussed more fully.

Table 7.1. Results for neuropsychological tests (with standard deviations) for DAT patients and controls. Differences are expressed as t-values (DAT patients vs. controls).

Memory subcomponent	Test	Controls *n=30*	DAT *n=33*	t-Value (P-value)
Premorbid IQ	NART IQ	114.4 (7.8)	113.2 (9.3)	0.5
Global	MMSE	29.5 (0.7)	23.5 (4.1)	8.1***
Working	Digit span	6.0 (0.7)	5.4 (0.9)	2.9**
	Della Sala dual performance	-1.4 (2.2)	-6.3 (10.3)	2.6
	Test of everyday attention	-1.0 (2.0)	-140.0 (403.9)	1.9
	Letter fluency	38.9 (13.0)	29.6 (12.4)	2.9**
Episodic	Logical memory immediate recall	9.9 (2.8)	3.9 (2.2)	9.5***
	Logical memory delayed recall	8.8 (3.0)	0.9 (1.5)	13.4***
	CERAD immediate recall	7.6 (1.3)	3.8 (1.7)	8.5***
	CERAD delayed recall	6.7 (1.7)	1.2 (1.5)	13.4***
	CERAD recognition	9.7 (0.5)	7.3 (1.6)	8.1***
	Doors & People verbal recall	8.9 (2.9)	4.1 (1.0)	13.6***
	Doors & People verbal recognition	9.7 (3.4)	5.0 (2.5)	5.6***
	Doors & People nonverbal recall	10.1 (4.5)	4.1 (2.6)	11.9***
	Doors & People nonverbal recognition	9.1 (3.4)	4.9 (2.5)	8.3***
Autobiographical	Autobiographical fluency-names	26.8 (11.0)	8.7 (5.5)	8.4***
	Autobiographical fluency-events	16.5 (7.0)	6.3 (5.1)	6.6***
	AMI - personal semantic	60.0 (3.5)	44.4 (10.9)	7.5***
	AMI - incident	21.7 (5.0)	11.6 (6.6)	6.8***
Remote	Famous face recognition	43.0 (6.7)	37.8 (9.4)	2.5
	Famous face identification	39.3 (8.8)	25.9 (10.2)	5.6***
	Famous faces naming	31.0 (9.2)	10.9 (7.5)	9.5***
	Famous name recognition	49.7 (0.7)	48.0 (3.1)	2.9**
	Famous name identification	49.1 (1.3)	40.7 (6.4)	7.1***
Semantic	Category fluency	114.4 (24.5)	73.9 (23.5)	7.7***
	Picture naming	48.0 (0.2)	41.0 (4.1)	9.2***
	Word-picture matching	48.0 (0.0)	46.9 (2.2)	2.7**
	Naming to description	22.9 (1.0)	19.0 (3.8)	5.4***
	Pyramids & Palm Trees	52.0 (0.2)	49.0 (3.0)	5.5***

Key

** P-value <0.01

*** P-value <0.001

Discriminant analysis of group membership

To determine how useful the battery of neuropsychological tests of memory was in differentiating patients with early DAT from controls, I entered the results of all neuropsychological tests for the two groups into a stepwise logistic regression analysis (see Table 7.2). This procedure allows one to determine the maximum prediction of group membership with the minimum number of variables significantly contributing to that group separation. It was found that one test, (delayed verbal recall of the Doors and People Test) could correctly classify patients in 96.8% of cases. It should be noted that my DAT group as a whole has very mild disease, with half of them having MMSE scores of 24 and above, conventionally taken as the cut-off for normality. Thus, one measure of anterograde episodic memory was able discriminate even DAT patients with mild disease from controls with a high degree of accuracy.

Table 7.2. Logistic stepwise regression analysis of neuropsychological tests for classification of DAT patients and controls

Classification table for subject group

		Predicted		
		Control	DAT	Percent correct
Observed	Controls	29	1	96.67
	DAT	1	32	96.97
			Overall	96.83

Chi Square 55.2, $p<0.0001$

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
D&P verbal recall	-1.3	0.38	11.6	1	0.0006	-0.33	0.28
Constant	4.1	1.22	11.2	1	0.0008		

Use of neuropsychological measures in staging

To assess the use of neuropsychological measures of memory in staging disease severity, I entered the memory tests as independent variables into a stepwise regression analysis to predict MMSE. The results are shown in Table 7.3. It can be seen that five tests (Della Sala *et al*'s dual performance task, immediate recall of logical memory, AMI incident memory, the Pyramids & Palm Trees Test and digit span, in decreasing order of importance) together predicted 70% of the variance in MMSE. Thus measures of immediate recall, working memory, autobiographical memory and semantic memory were of use in staging DAT. It is interesting that delayed recall, which is the best discriminator between DAT and controls, is of no use for staging on account of floor effects reached early in the illness. By contrast, measures of working memory are of little help in diagnosis but are valuable in the assessment of disease severity.

Table 7.3. Stepwise regression analysis using memory measures as independent variable to predict dementia severity as measured by MMSE

Component of memory	Test	R-squared
Working	Della Sala dual performance	0.36
Episodic	Logical memory - immediate	0.48
Autobiographical	AMI - incident	0.55
Semantic	Pyramids & Palm Trees	0.62
Working	Digit span	0.70

Comment

I have found that neuropsychological tests of memory are of use, both in discriminating patients with minimal DAT from controls, and in staging the illness. Those tests of most use in diagnosis are different from those of value in staging. This relates to the fact that some aspects of memory show floor effects early in the disease process.

Experiment 2 - SPECT imaging

Methods

Subjects

Two groups consisting of a total of 55 subjects participated in the SPECT study: 31 patients with DAT and 24 "controls". While the 31 DAT patients were from the 33 given the neuropsychological test battery, the 24 "controls" were different from the control subjects used in the neuropsychological part of the study. Further details of these subject groups are given in Chapter 2.

SPECT imaging

Details of SPECT imaging data acquisition and analysis are presented in Chapter 2.

Statistical analysis

To determine whether there were differences in rCBF for each ROI, corrected to occipital rCBF, between DAT patients and controls, unpaired comparisons using Student's t-test were used. Next, a repeated measures Analysis of Variance was performed to assess whether any significant differences were attributable to region of interest, to group (DAT vs. control group), or to interaction between the two. A significant effect of group or region of interest, would indicate that the differences in the means between the two groups, or between the regions of interest, respectively, were greater than expected from the inherent variance of the data. A significant interaction of factors would indicate that there was a disproportionate difference between the groups in at least one region of interest.

A further logistic stepwise regression analysis was used to determine the maximum prediction of group membership with the minimum number of variable significantly contributing to the group separation, i.e. to ascertain the ability of SPECT scanning to correctly classify DAT patients and controls.

To assess the role of SPECT in staging DAT severity, stepwise linear regression analysis was used. The independent variables, rCBF for each region of interest, were used to determine severity as measured by MMSE.

In studying how many of my DAT patients had normal SPECT scans, rCBF for each ROI for each DAT subject were expressed as Z-scores by comparing them with controls' data. Any Z-score less than -1.96 was taken to be abnormal, this representing two standard deviations from the mean of the controls.

Results

A comparison of rCBF for each ROI in the DAT patients and controls is shown in Table 7.4. An ANOVA with repeated measures indicated significant subject group ($F(1,53)=9.1$, $p<0.005$) and region of interest effects ($F(11,583)=14.5$, $p<0.0001$) as well as a group by ROI interaction ($F(11,583)=2.2$, $p<0.05$). This indicates that DAT is selectively affecting certain regions of interest, rather than affecting blood flow as a

whole. On account of this, unpaired comparisons were calculated for each ROI, and the results are shown in Table 7.4. It can be seen that only 6 of the 12 ROIs (five right and one left) showed a significant difference between DAT patients and controls: right frontal, right high frontal, right temporal, right parietal, right posterior temporal, and left frontal.

Table 7.4. SPECT ROI rCBF corrected to occipital rCBF for DAT patients and controls (with standard deviations). Differences between groups are expressed as t-values.

Region of interest	Controls *n=24*	DAT *n=31*	t-Values (P-values)
Right frontal	0.90 (0.06)	0.83 (0.08)	3.6***
Right high frontal	0.89 (0.06)	0.81 (0.09)	3.5***
Right temporal	0.87 (0.05)	0.82 (0.08)	2.7**
Right parietal	0.90 (0.06)	0.85 (0.08)	2.6*
Right posterior temporal	0.92 (0.05)	0.88 (0.06)	2.5*
Left frontal	0.89 (0.06)	0.84 (0.08)	2.4*
Left temporal	0.89 (0.06)	0.86 (0.08)	1.9
Left high frontal	0.88 (0.07)	0.84 (0.10)	1.7
Left hippocampal	0.82 (0.06)	0.78 (0.09)	1.7
Right hippocampal	0.83 (0.06)	0.80 (0.09)	1.5
Left parietal	0.89 (0.05)	0.87 (0.07)	0.7
Left posterior temporal	0.88 (0.06)	0.89 (0.06)	-0.2

Key

* P-value <0.05

** P-value <0.01

*** P-value <0.001

Discriminant analysis of group membership

To study how useful SPECT was in discriminating between controls and DAT patients, the ROIs were entered into a stepwise logistic regression analysis with backward elimination (see Table 7.5). This analysis resulted in correctly predicted group membership in 75% of cases using two ROIs, viz. right high frontal and right posterior temporal.

Table 7.5. Logistic stepwise regression analysis of SPECT ROIs for classification of DAT patients and controls

Classification table for subject

		Predicted		
		Control	DAT	Percent correct
Observed	Control	16	8	66.67
	DAT	6	25	80.65
			Overall	74.55

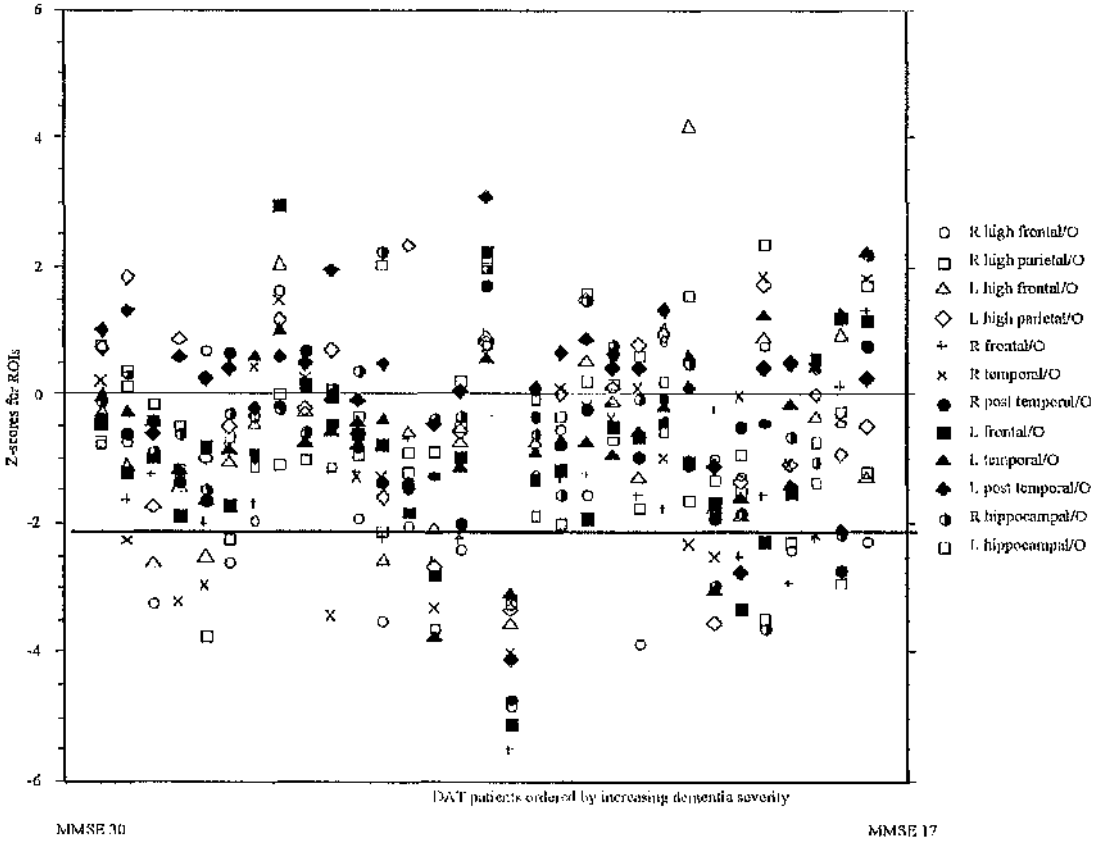
Chi Square 12.6, p=0.0004

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
Right high frontal	-12.8	5.09	6.35	1	0.01	-0.24	0.00
Right posterior temporal	-18.1	8.33	4.70	1	0.03	-0.19	0.00
Constant	7.6	6.22	1.49	1	0.22		

Proportion of normal SPECT scans in DAT patients

To examine the related issue of how many of my DAT patients had normal SPECT scans, I studied rCBF for each of the 12 ROIs, expressed as Z-scores with reference to normal controls. As can be seen in Figure 7.1, 19 of 31 patients (61%) fell outside the normal range on at least one of the indices of abnormal rCBF patterns. Twelve of my 31 patients (39%) had entirely normal SPECT scans (i.e. normal rCBF for each of the 12 ROIs). Those with normal scans tended to be most mildly affected by DAT. However, some of my patients with more established disease, as defined by MMSE, also had normal SPECT scans. Thus a significant number of patients with early DAT had entirely normal SPECT scans, highlighting the limited sensitivity of SPECT in diagnosing DAT.

Figure 7.1. Regional cerebral blood flow for regions of interest (ROIs) for DAT patients ordered by increasing dementia severity according to MMSE score (30-17), expressed as Z-scores



Use of SPECT in staging disease severity

To study the use of SPECT in staging DAT, a correlation analysis showed that no ROI significantly correlated with dementia severity as determined by MMSE ($p>0.05$). I entered the ROIs as independent variable into a stepwise regression analysis in order to predict severity of dementia as defined by the MMSE (see Table 7.6). All ROIs together could account for 38% of the variance in MMSE score. Those ROIs of most importance in determining severity can be seen in Table 7.6, in decreasing order of importance. SPECT is thus of limited use in staging DAT severity as measured by the MMSE.

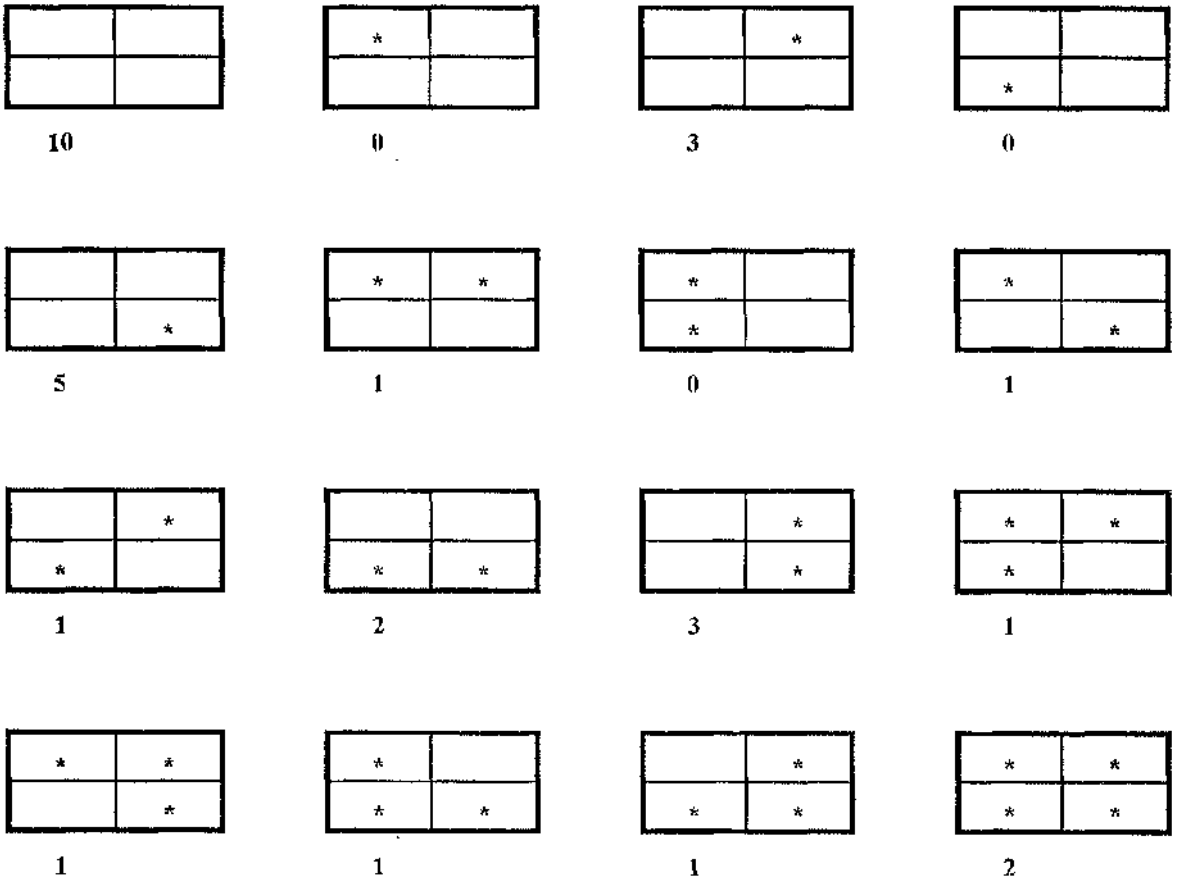
Table 7.6. Stepwise regression analysis using SPECT ROI rCBF corrected to occipital rCBF as independent variables to predict dementia severity as measured by MMSE

Region of interest	R-squared
Left temporal	0.11
Left posterior temporal	0.28
Left high parietal	0.32
Left high frontal	0.33
Right parietal	0.34
Right posterior temporal	0.36
Right high frontal	0.37
Left parietal	0.37
Right frontal	0.37
Right temporal	0.38
Right hippocampal	0.38
Left frontal	0.38

Pattern of rCBF impairment in DAT

Figure 7.2 illustrates the possible patterns of rCBF impairment. Of the possible permutations of rCBF, only three patterns of rCBF did not occur in my DAT group: isolated left anterior hypoperfusion, isolated left posterior hypoperfusion and combined left anterior and left posterior hypoperfusion. By this method, ten of 31 scans (32%) were normal for all regions, 8 showed an abnormality in one region, 7 had abnormalities in 2 regions, 4 had 3 abnormal regions, and 2 had abnormalities in all regions. Posterior deficits were seen in 18 of 31 patients (58%); 15 patients showed anterior deficits (48%). Anterior hypoperfusion occurred almost as commonly as did posterior hypoperfusion, and 4 of 31 patients (13%) exhibited anterior hypoperfusion in the absence of any posterior hypoperfusion. The classical pattern of purely posterior temporoparietal hypoperfusion occurred in only 7 of 31 (23%) of patients.

Figure 7.2. Abnormal rCBF patterns in the 31 patients with probable Alzheimer's disease. The number of patients are shown below each pattern. A pronounced heterogeneity of rCBF patterns is seen.



Key

LF	RF
LP	RP

x	No. of patients with rCBF pattern
LF	left frontal
LP	left posterior
RF	right frontal
RP	right posterior

Comment

I have found SPECT to be of limited use in the diagnosis of DAT, especially in minimal disease. SPECT was also of limited use in staging DAT, at least as studied in patients with MMSE scores of 30-17. In contrast to the accepted wisdom that DAT causes temporoparietal hypoperfusion early in the disease, I found that the pattern of

rCBF deficit was much more heterogeneous, with anterior hypoperfusion occurring almost as frequently as posterior hypoperfusion.

Discussion

Prior to discussing my findings, I would draw attention to one limitation of all *in vivo* research on DAT. This relates to the inability to make a certain diagnosis of DAT in living subjects. A definitive diagnosis of DAT can only be made by autopsy, or biopsy which in the majority of cases is unnecessary and unethical. Existing studies of functional imaging rely on clinical criteria to establish a diagnosis of probable DAT; however, only 40 of around 500 patients studied with PET have come to autopsy for pathological confirmation of the diagnosis [180]. I have used a well standardised set of clinical criteria (NINCDS-ADRDA [219]) shown to be at least 80% accurate in predicting DAT pathology [50, 231]. These criteria make use of neuropsychology as supportive evidence for diagnosing probable DAT. Thus, any direct comparison of neuropsychology and SPECT is perhaps not really valid, as neuropsychology is employed in the diagnostic criteria. It should be noted, however, that the neuropsychological tests employed in the current study were quite different from those which are taken into account in the clinical diagnosis.

I confirmed the prime role of neuropsychological tests of memory in discriminating patients, even in minimal disease, from controls. Of the various measures used, delayed recall of verbal material was the best discriminator, whereas tests of working memory, semantic memory and immediate recall, were of use in staging DAT. The finding that those memory tests of use in diagnosis are of less benefit in staging, and vice versa, has been well described [304, 352, 353], and is due to the fact that some components of memory, such as delayed recall, achieve a floor effect early in disease, while other components of memory continue to deteriorate and are thus of use in staging.

In general, I found SPECT of more limited value in diagnosing patients in the very early stages of DAT. Using logistic regression, 74% of my subjects could be correctly classified, in distinction to neuropsychology correctly classifying 98% of subjects. This is highlighted by the fact that many of my patients with abnormal neuropsychology had normal SPECT scans. Previous studies have shown better discriminative ability of SPECT, but have tended to recruit patients with well established disease. Reed *et al*'s study is perhaps the one most directly comparable with ours, in that they studied patients with early DAT, some of whom exhibited abnormal neuropsychology but had normal SPECT scans [266].

With regard to the ROIs affected in DAT, I found that right high frontal and right posterior temporal rCBF were of most use in discriminating DAT subjects from controls. While most studies have found temporal and parietal blood flow to be consistently reduced in DAT [164, 230, 320], others have found more widespread

involvement, although with temporo-parietal changes tending to be most marked [171, 218, 246]. These studies are largely compatible with early DAT causing temporo-parietal hypoperfusion, with frontal hypoperfusion occurring in more extensive disease. In keeping with this, Reed *et al* [266] found left temporal and right temporal hypoperfusion in their mild DAT patients, and that moderate patients had impaired dorsolateral frontal rCBF with respect to mild patients. By contrast, Waldemar *et al* [340] found that there was no disproportionate reduction of rCBF in any brain region, and that DAT patients had significantly reduced blood flow in frontal, temporal, parietal and hippocampal regions. Interestingly, Cappa *et al* [61], in agreement with my study, found frontal as well as temporoparietal perfusion to be of most use in discriminating DAT subjects from controls.

In my cross-sectional study, SPECT was also shown to be of limited use in staging DAT: some of my patients had MMSE scores as low as 17, yet had scans within normal limits. Other cross-sectional studies comparing rCBF with dementia severity have produced conflicting results; in some studies, MMSE has correlated with temporal rCBF [164, 166], but used DAT patients with more advanced disease. In another study, MMSE correlated with frontal and parietal, but not temporal rCBF which was impaired in both mild and moderate DAT [99]. Wolfe *et al* [362] were in agreement with my study in finding that temporal lobe rCBF did not significantly correlate with MMSE. However, they extended their study by assessing their subjects longitudinally, and found a significant correlation between temporal lobe rCBF and the rate of decline in MMSE. In a similar study using PET, Smith *et al* [300] also found a correlation between functional imaging and the longitudinal course of cognitive decline. It is likely that correlations between dementia severity and rCBF may only be detected by such more powerful longitudinal studies rather than by cross-sectional studies such as this.

Other explanations for the discrepancies between studies include variability in sophistication of SPECT scanning equipment, and in methods of image analysis (e.g. choice of anatomical regions for rCBF), and statistical analysis. SPECT scanning equipment varies in sophistication. While my images were acquired using a single camera, other means of image acquisition employ dual cameras, or even multi-detector scanning using sets of scintillation detectors with focusing collimators, which produce brain tomographs with image quality comparable with PET scanners [230]. My ROIs were drawn by hand with reference to an anatomical atlas [9]. I was not able to utilise current techniques which allow lateral and anterior-posterior deformation of the rCBF pattern to conform to a standardised template, and thus produce more accurate results [77]. Another source of variation between studies is the choice of reference rCBF. Although some investigators normalise rCBF to the cerebellum, other investigators normalise rCBF to the occiput, as in my study. There is also variation between

studies in the method of statistical analysis, with increasingly sophisticated techniques improving the diagnostic yield of SPECT scanning [170].

My other main finding with SPECT related to the variability of rCBF defects seen in DAT, indicative of the heterogeneity of distribution of DAT pathology. Most studies have shown temporoparietal changes in DAT [51, 157, 241]. However, I have demonstrated that frontal hypometabolism occurs almost as often as posterior hypometabolism. These results are in keeping with Waldemar *et al* [340], who found considerable heterogeneity in rCBF in DAT, as measured by HMPAO-SPECT, affecting both posterior and anterior structures. They also noted that frontal deficits occurred more frequently than previously reported; indeed, 8% of their patients exhibited solely frontal hypometabolism.

It has previously been suggested that purely frontal hypometabolism on SPECT is against a diagnosis of DAT, and more in keeping with dementia of frontal type or progressive supranuclear palsy [241]. Indeed, it might be argued that some of my patients with anterior hypoperfusion have focal lobar atrophy (Pick's disease). I attempted, however, to exclude such patients by selecting those with insidious progressive memory impairment, classical of DAT. None of my patients presented with predominant personality change, apathy or other behavioural changes suggestive of focal lobar atrophy. I thus feel that my cases with anterior hypoperfusion on SPECT are very likely to have Alzheimer pathology, and that the observed heterogeneity of distribution of rCBF changes is real.

There are two reasons why the results of comparing neuropsychology and SPECT, for diagnosis and staging, should be regarded with caution. Firstly, neuropsychological assessment is contributory to the initial clinical diagnosis of probable DAT. Patients only present when there is a clinical complaint, which will almost certainly be associated with neuropsychological abnormalities. It is generally thought that patients presenting early in the course of DAT, with memory impairment, have pathology affecting perihippocampal structures, thus deafferenting the hippocampus [42]. Although sufficient to cause clinically significant memory impairment, the pathology may not be extensive enough to cause functional imaging deficits. I suspect that those patients of ours with abnormal neuropsychology and normal SPECT may have localised perihippocampal pathology which is insufficiently extensive to be detected by SPECT. Advances in SPECT technology may lead to greater resolution sufficient to show less extensive pathology. However, even high-resolution PET studies have shown substantial individual variability in the degree of medial temporal lobe hypometabolism in DAT [165].

Secondly, it is also conceivable that, in other circumstances, DAT pathology might be sufficiently extensive to cause SPECT abnormalities, yet, depending on which anatomical sites are affected, may remain "clinically silent". Such patients would have abnormal SPECT, but would be clinically asymptomatic. They would not

present to a Memory Disorders Clinic. Thus my DAT group may not be truly representative of subjects with DAT pathology, but only of those whose disease clinically manifests, and leads to presentation at a memory clinic.

Another issue to be considered here is the selection of controls in the two experiments: those used for the neuropsychological comparison were different from the controls used in the SPECT study. It should be borne in mind that my SPECT study did not use true normal volunteer controls, which I felt was ethically unacceptable, given the radiation doses involved. For controls, I used subjects presenting to the memory clinic who were felt to have non-organic pathology as a cause of their memory complaints. Some of these subjects had psychiatric disorders such as depression contributing to their memory impairment, and it is known that depression [30] and other psychiatric disorders such as schizophrenia [200] may have abnormalities on functional imaging. I excluded from my study patients with clinically major depression, schizophrenia and obsessive-compulsive disorder, but even by using patients with minor psychiatric illnesses who could conceivably have abnormal SPECT scans, there is the danger of introducing a type II error. That is to say, some of my DAT patients may be incorrectly classified as having normal SPECT scans as a result of being compared to such "control" scans. I admit that this criticism is valid, but could only be circumvented by SPECT scanning age-matched healthy volunteers. In fact, my apparent error in using such subjects rather than normal controls may highlight a clinical point. That many of my DAT patients had SPECT scans no different from patients with non-organic pathology, presenting to a memory clinic, indicates that SPECT scanning sometimes does *not* help the clinician in deciding whether a patient with possible memory impairment has organic or non-organic pathology. Despite these caveats, the fact remains that some of my DAT patients, who have abnormal neuropsychology, had "normal" SPECT scans.

Even if it could be ascertained that neuropsychology was genuinely more sensitive than SPECT for diagnosing DAT, this would perhaps be not surprising. Neuropsychological tests are a type of activation study, requiring the utilisation of various cognitive processes to achieve a particular task. My SPECT images, by contrast, were of resting rCBF. It may be that some of my patients with minimal DAT have pathology insufficient to cause a resting rCBF deficit, but might have shown regional hypoperfusion on an activation task. An analogy might be drawn with thallium cardiac scanning, in which myocardial ischaemia might be detected only on exercise. Impairments on activation studies in DAT have been shown by both PET [223] and SPECT [271]. Thus a comparative study of neuropsychology and SPECT activation studies might better address the issue of the relative sensitivity of neuropsychology and SPECT in the diagnosis of DAT.

Summary

I studied the role of neuropsychology in diagnosis and staging dementia of Alzheimer type (DAT). A neuropsychological battery of tests of working, episodic, semantic and remote memory was administered to 33 patients with mild DAT and 30 matched controls. For diagnosis, it was determined by logistic regression analysis that one of the memory tests (delayed verbal recall of the Doors and People Test) could correctly classify subjects as DAT or controls in 97% of cases. For staging, stepwise regression analysis using five of the memory tests could predict 70% of the variance in MMSE scores. The measures most useful for staging were tests of immediate recall, and tests of working, semantic and autobiographical memory.

In a separate experiment, SPECT imaging on 31 of the above 33 patients and 24 different controls was used to address the issue of diagnosis and staging. 99Tc-HMPAO SPECT scans were analysed quantitatively to obtain measures of regional cerebral blood flow (rCBF). Logistic regression analysis showed that two of the SPECT ROIs (right high frontal and right posterior temporal) could correctly classify subjects in 75% of cases. Of note was the fact that 39% of the DAT patients had normal SPECT scans. SPECT data were of limited use in modelling disease severity; only 38% of the variance in MMSE scores could be predicted from SPECT data. In addition, I found that the pattern of rCBF in DAT was much more heterogeneous than previously described.

Chapter Eight

The value of longitudinal assessment of components of memory in staging dementia of Alzheimer type

Introduction

This chapter continues the theme of the relative value of neuropsychology in the diagnosis and staging of DAT but considers the longitudinal data collected on the patient cohort.

As discussed already, a number of cross-sectional studies have found that delayed recall is of use in diagnosis, while staging the disease was better achieved by measures of working and semantic memory, and visuo-spatial function [353]. The results from my cross-sectional data, as detailed in Chapter 7, were in agreement with this.

There are, however, methodological advances in utilising a longitudinal approach to study the diagnosis and staging of DAT. Previous longitudinal studies in DAT have measured decline by cognitive scales [49, 315, 322] (e.g. CAMCOG [279]), global ratings of clinical severity [35, 178] (e.g. Blessed IMC test [37]) and functional end-points [95, 139]. The small number of studies using more detailed neuropsychological measures to assess cognitive impairment longitudinally have focused on the order of progression of domains of cognition (i.e. memory vs. language vs. visuoperceptual function) rather than domains of memory [28, 118].

Longitudinal studies of normal elderly to detect early DAT

Katzman *et al* [177] studied a cohort of elderly community-dwelling subjects prospectively, and found that the best predictor of subsequent development of DAT was poor performance on the Information-Memory-Concentration Test of Blessed *et al* [37]. In contrast, LaRue and Jarvik [196, 197] found that a measure of abstract reasoning was a better predictor of subsequent dementia. Early impairment of episodic memory has been noted to be a harbinger of DAT in other longitudinal studies [317, 358]. Similarly, in a longitudinal study of elderly subjects in the community, Linn *et al* [201] found that measures of long-term verbal memory were of most use in detecting subjects with very early DAT.

Longitudinal studies of DAT subjects to stage progression of disease

As in cross-sectional studies, those employing a longitudinal methodology have shown that those cognitive measures of most use for diagnosing DAT were of least use for monitoring disease progression. For instance, although delayed recall is of use in diagnosis, such anterograde episodic measures show a floor effect early in DAT [176, 304], and hence are of limited use in staging. Other subcomponents of memory are of greater value in showing longitudinal decline.

In Botwinick *et al*'s longitudinal study of DAT [40], the tests showing the greatest decline over 4 years were the logical memory, the digit symbol and the Trailmaking tests. It is perhaps surprising that logical memory should show a decline rather than floor effects. The authors do not stipulate which component of the logical

memory test is reported, and this may relate to the immediate recall component, which shows less of a floor effect early in the disease than does delayed recall. The digit span forward subtest of the WMS showed the least decline.

Mohs *et al* [224] found that tests on which the patient exhibits an intermediate degree of impairment are most likely to be sensitive to the progressive worsening over a year, as these avoid ceiling and floor effects. Learning low-frequency paired associates and recall (difficult tasks) and naming common objects (an easy task) were both insensitive to change. Scores on tasks of intermediate difficulty, including sentence reading, recognition and paired-associated learning, were sensitive to change over a year.

More recently, Morris *et al* [232] reported part of the longitudinal component of the CERAD study of DAT which employs both well established cognitive scales, and tests of memory, language and visuospatial ability. Verbal memory was assessed using a word-list learning task with recall and recognition components, and semantic memory by verbal fluency and naming tasks. There was, however, no assessment of working memory or remote memory. They did not focus on patterns of impairment of subcomponents of memory, but rather used the overall data to address the rate of decline: this appeared to be non-linear, with less severe dementia showing a slower rate of decline.

There have been very few longitudinal studies of DAT using detailed cognitive neuropsychology tests, and these have tended to focus on selected subcomponents of memory. Baddeley *et al* [14] studied working memory, and found that the central executive component deteriorated over one year in a cohort of DAT patients. Episodic and semantic memory were studied over one year by Hodges *et al* [146], who found that measures of semantic memory (naming, number information, similarities and category fluency) showed a more rapid rate of decline in a group of DAT patients than in a matched Huntington's disease group. In a further study, Hodges *et al* [147] studied picture naming in DAT over three years, and found that the pattern of deterioration in naming was consistent with a progressive deterioration in semantic knowledge. To my knowledge, there have been no previous longitudinal studies of remote memory in DAT.

Aims

I wished to address the following question:

Which components of memory deteriorate over a one year period in patients with initially minimal and mild DAT ? This question is of relevance to the use of memory measures in staging DAT.

Methods

Subjects

Thirty-three DAT patients were tested at year 1. Twenty-four of the original 33 DAT patients were retested after one year. Five patients did not wish to be retested, three were no longer able to be tested at year 2 on account of the severity of DAT, and one sustained a cerebro-vascular accident after the first round of testing, and was withdrawn from the study. The three patients who were withdrawn due to inability to comply with testing were among the most severely affected at year 1. Their removal from the analysis will lead to a tendency to underestimate the longitudinal deterioration in the most severe group (here termed mild, MMSE 17-23).

In might be argued that any deterioration in the DAT group over one year could be attributable to the effects of ageing, rather than the progression of DAT. In an attempt to refute this, I retested five of the controls after one year. There was no evidence of any longitudinal deterioration on any of the tests. I felt, therefore, fairly confident when attributing any significant deterioration in neuropsychological performance in the DAT patients over one year to disease progression and not to ageing.

Tests

Details of the neuropsychological tests administered are given in Chapter 2.

Statistical analysis

To assess which components of memory deteriorated significantly over one year, paired comparisons using t-tests were calculated. A Bonferroni correction was applied on account of the number of comparisons. This was done for both the minimal and mild DAT subgroups.

Results

Staging DAT

The longitudinal data allows one to monitor which aspects of memory deteriorate in the minimal and mild groups. Table 8.1 illustrates performance on memory measures by the minimal and mild groups at year 1 and year 2. The scores for year 1 are based on the 24 DAT patients who were tested longitudinally, and are different to the data in previous chapters, where mean scores were derived from the 33 DAT patients tested at year 1.

Minimal DAT

Table 8.1 illustrates those components of memory which deteriorated significantly over one year in the minimal group. Although there was a trend for working memory tests to deteriorate, none of the analyses reached significance over one year. Similarly, none of the components of episodic memory showed a significant decline with time.

The component of memory which showed the most striking deterioration over one year was remote memory. Although the autobiographical measures did not deteriorate significantly, the face and name identification subcomponents of the remote memory tests showed a significant decline. This is in keeping with loss of semantic knowledge regarding famous people. Of the general semantic tasks, none deteriorated significantly over one year.

In summary, longitudinal study of minimal DAT patients showed a significant deterioration only for remote memory for famous figures, in particular for face and name identification.

Mild DAT

Again it can be seen from Table 8.1 which components of memory deteriorated most over one year in the mild DAT group. Surprisingly, none of the working memory measures deteriorated significantly over one year. On the whole, there was no significant decline on the measures of anterograde episodic memory, with the exception of immediate recall on logical memory. This is due to the fact that on all other measures, particularly those of delayed recall, performance was already so poor at year 1 that there was no scope for further decline. On the tests of remote memory, there was a difference between the autobiographical measures which, with the exception of the personal semantic component of the AMI, showed no change, and the famous face and famous name identification tests which demonstrated a significant decline. Again this is almost certainly due to the near floor performance on the tests of autobiographical memory at year 1. There was a significant deterioration in general semantic memory as measured by category fluency, but not for picture naming, word-picture matching, naming to description or the Pyramids and Palm Trees Test.

In summary, mild DAT patients followed longitudinally showed evidence of deterioration on tests of the immediate recall component of episodic memory, the personal semantic component of the AMI, famous face and famous name identification and category fluency.

Table 8.1. Longitudinal neuropsychological test data for minimal and mild DAT patients (with standard deviations), with degree of significance

	Minimal DAT	*n=12*	Mild DAT	*n=12*
Year	1	2	1	2
MMSE	26.3 (1.8)	25.4 (2.9)	21.5 (1.7)	21.7 (2.9)
Working				
DS dpt	-3.0 (4.5)	-5.1 (6.5)	-5.8 (5.6)	-4.5 (6.8)
TEA	-10.7 (29.8)	-8.2 (21.0)	-248.0 (611.0)	-513.9 (977.0)
Letter fluency	35.0 (10.0)	31.9 (14.7)	20.1 (8.7)	20.2 (15.0)
Episodic				
Log M imm	9.9 (4.5)	7.8 (4.3)	6.7 (3.9)	4.4 (4.2)***
Log M del	3.4 (4.4)	1.2 (1.9)	1.2 (1.8)	1.2 (1.5)
CERAD del recall	1.7 (1.5)	2.0 (2.8)	0.7 (1.5)	0.5 (0.8)
CERAD recog	7.6 (1.5)	7.8 (1.4)	7.2 (1.8)	6.5 (1.9)
DP verbal recall	4.3 (1.4)	3.9 (1.5)	3.9 (0.7)	3.2 (0.8)
DP verbal recognition	5.8 (3.0)	5.4 (2.5)	4.2 (2.6)	4.2 (2.2)
DP nonverbal recall	5.4 (2.7)	4.4 (2.5)	2.8 (1.6)	2.4 (0.9)
DP nonverbal recognition	5.6 (1.4)	4.6 (2.2)	4.2 (1.4)	4.0 (1.9)
ABM				
ABF - names	9.3 (4.7)	7.6 (5.2)	8.2 (6.1)	7.6 (5.1)
ABF - events	7.8 (5.4)	7.5 (5.0)	5.0 (4.1)	4.7 (2.9)
AMI - psem	46.7 (9.4)	43.9 (9.2)	43.3 (12.0)	40.1 (11.9)*
AMI - incident	10.8 (7.0)	9.7 (6.6)	11.4 (6.6)	11.1 (6.9)
Public				
FF recog	35.7 (11.5)	41.1 (8.6)	38.7 (8.6)	38.5 (10.8)
FF ident	24.0 (9.6)	20.2 (9.4)*	27.0 (11.8)	22.7 (12.6)**
FF naming	8.0 (4.7)	7.5 (5.2)	12.8 (9.0)	11.3 (9.6)*
FN recog	48.2 (1.4)	47.6 (3.3)	47.8 (3.6)	46.7 (3.1)
FN ident	41.7 (4.6)	33.2 (8.9)**	39.1 (7.3)	31.0 (9.3)***
Semantic				
Category fluency	72.5 (22.6)	65.2 (37.0)	55.8 (14.6)	44.2 (24.7)*
Picture naming	42.1 (3.1)	42.3 (5.9)	37.8 (3.1)	41.3 (5.7)
Word-picture matching	47.3 (0.9)	47.0 (1.3)	46.2 (3.4)	46.9 (1.6)
Naming to description	20.4 (4.1)	18.8 (4.9)	17.5 (3.2)	18.6 (4.2)
PPTT	49.9 (1.9)	49.6 (4.2)	47.6 (3.6)	47.3 (5.4)

Key * $p<0.05$ ** $p<0.01$ *** $p<0.001$

Table 8.2. Summary of neuropsychological tests showing decline over one year for minimal and mild DAT subgroups

	Minimal DAT	Mild DAT
Episodic memory		Log M immediate recall
Autobiographical memory		AMI - personal semantic
Remote memory	FF identification	FF identification and naming
	FN identification	FN identification
Semantic memory		Category fluency

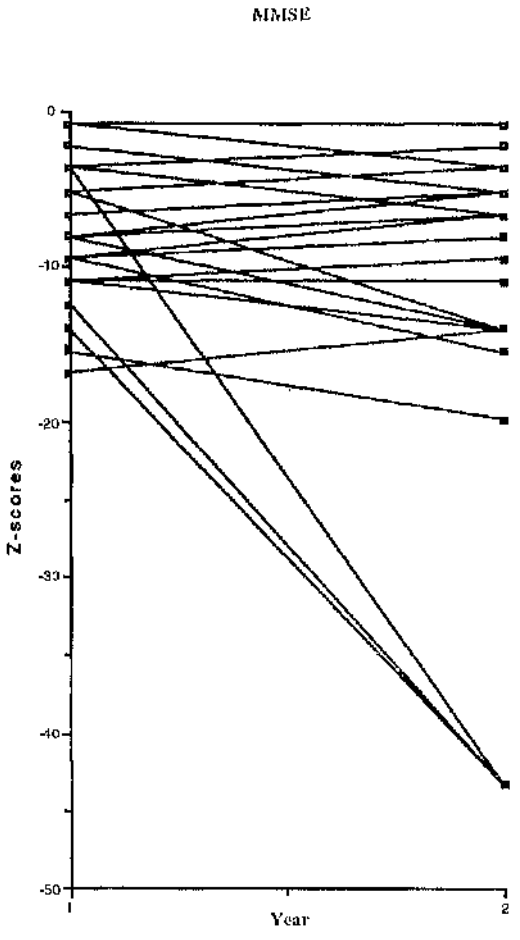
Inter-individual differences

Although the analysis of the change in performance of the patient groups gives an indication of the overall trends, these data almost certainly mask large individual differences. To investigate this aspect, I converted each patient's score on a number of selected tests to Z-scores (to allow comparability across tests) and plotted the change in Z-score over the period of the study. The tests were chosen to represent a cross-spectrum of those employed (e.g. one test of working memory, one of anterograde memory etc.) on which either the minimal or mild patients showed a significant decline.

Mini-mental state examination

Figure 8.1 shows each patient's performance on the MMSE. It can be seen that there was considerable heterogeneity. Most minimal cases change very little and a few showed a slight improvement (due perhaps to practise effects). One minimal and two mild cases showed a precipitous decline.

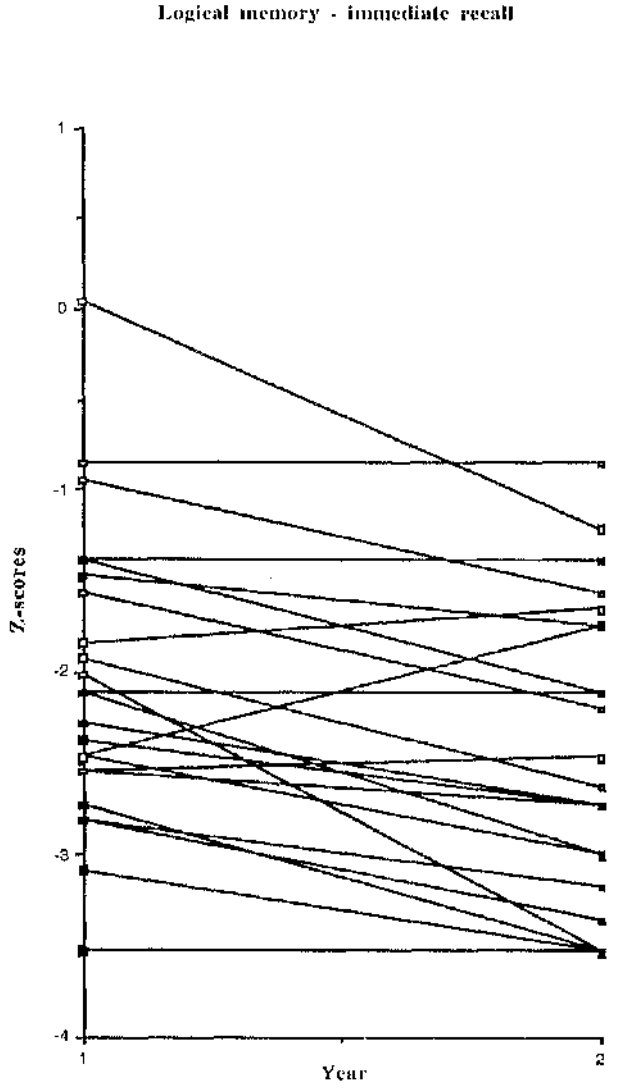
Figure 8.1. Longitudinal deterioration in MMSE over one year for individual DAT patients, expressed as Z-scores (minimal DAT: open boxes, mild DAT: closed boxes)



Episodic memory

Only the mild DAT patients declined significantly over one year on the immediate recall component of the logical memory test. It can be seen on an individual case basis that the decline is relatively uniform. Although one minimal patient shows an improved performance after a year, most of the individual cases show a mild decline.

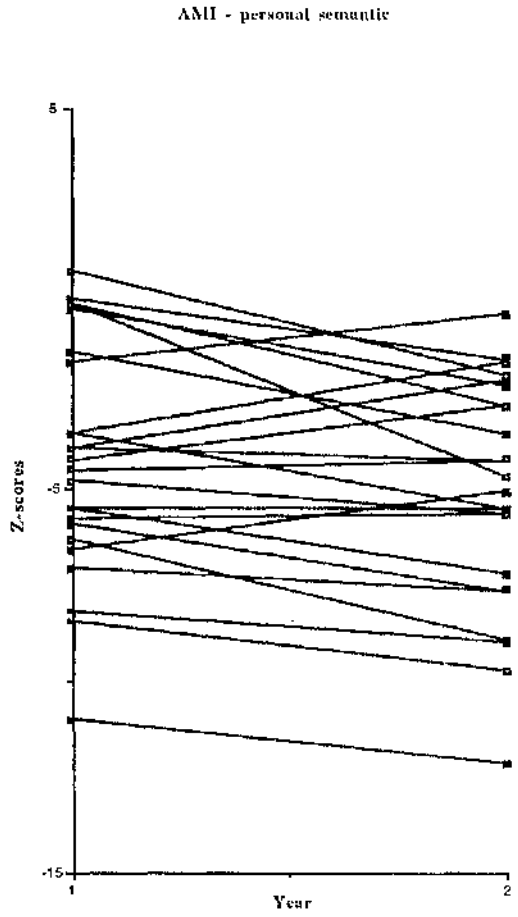
Figure 8.2. Longitudinal deterioration in logical memory immediate recall over one year for individual DAT patients, expressed as Z-scores (minimal DAT: open boxes, mild DAT: closed boxes)



Autobiographical memory

Although the minimal DAT group showed no significant decline over one year on the autobiographical memory tests, the mild DAT group did decline longitudinally on one of the tests, the personal semantic component of the AMI. Individual cases are shown in Figure 8.3. It can be seen that the decline is variable on a case-by-case basis. It is also notable that there is considerable overlap between the minimal (open boxes) and mild (closed boxes) DAT patients, indicating that autobiographical memory performance is not always strongly correlated with disease severity.

Figure 8.3. Longitudinal deterioration in personal semantic component of the AMI over one year for individual DAT patients, expressed as Z-scores (minimal DAT: open boxes, mild DAT: closed boxes)



Memory for public figures

It can be seen from Figures 8.4 and 8.5 that the overall pattern is of slow decline over one year, although there is some individual variation. Again it can be seen that there is overlap between minimal and mild DAT patients, some patients with mild DAT performing consistently better than the less globally demented minimal DAT patients.

Figure 8.4. Longitudinal deterioration in famous face identification over one year for individual DAT patients, expressed as Z-scores (minimal DAT: open boxes, mild DAT: closed boxes)

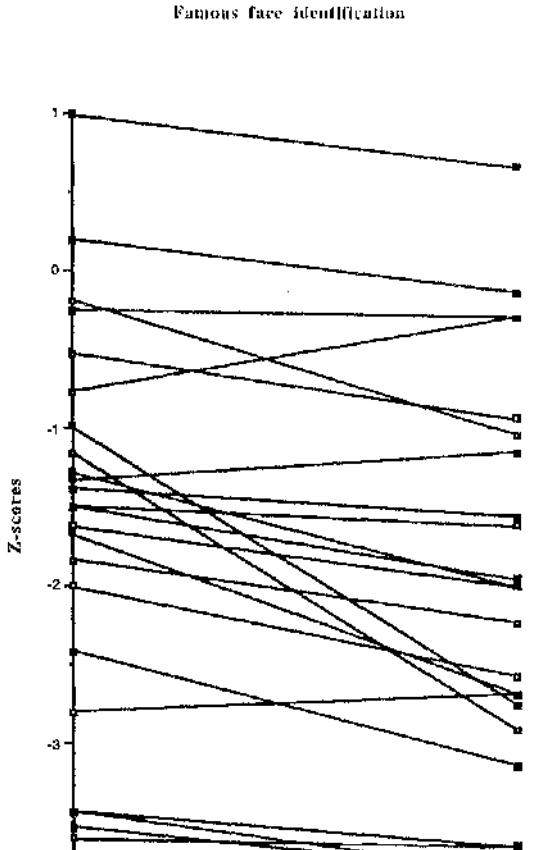
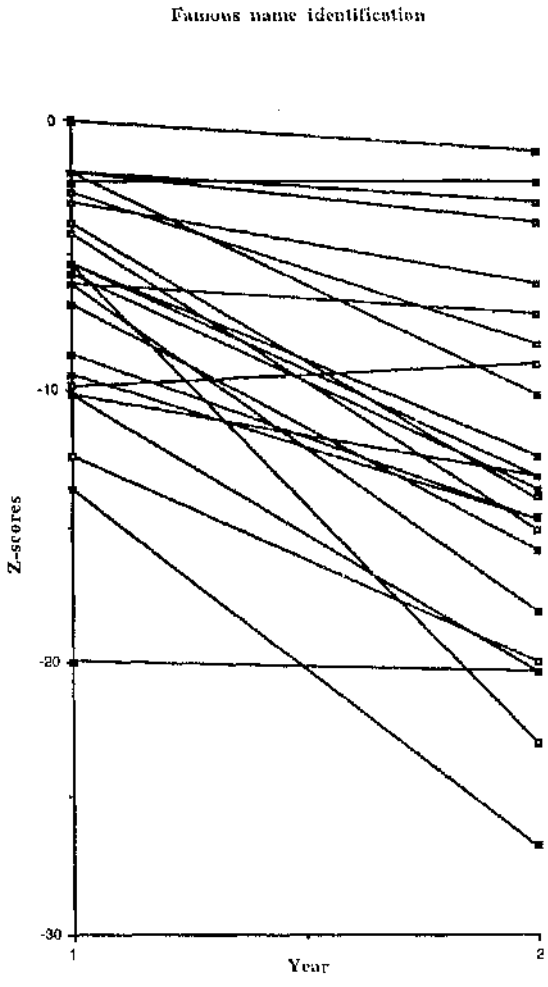


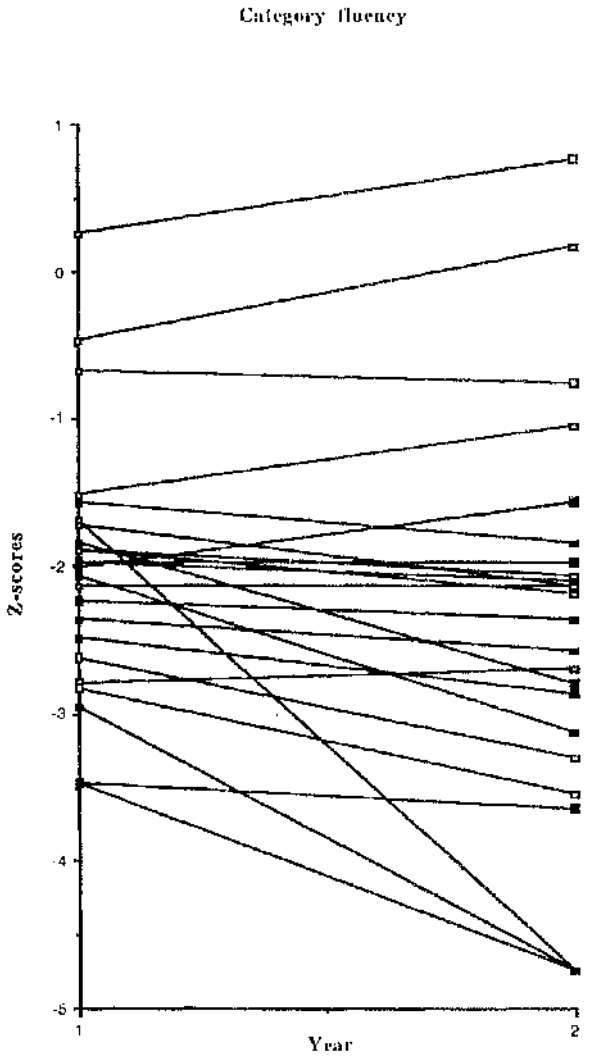
Figure 8.5. Longitudinal deterioration in famous name identification over one year for individual DAT patients, expressed as Z-scores (minimal DAT: open boxes, mild DAT: closed boxes)



Semantic memory

Once more, a pattern of mild decline, with some individual exceptions, is seen. It can also be seen that three of the four least impaired performers at year 1, who happen to have minimal disease, show an improvement over one year. It may be that practise effects are overcoming whatever semantic memory deterioration, if any, is occurring in these minimally affected DAT patients.

Figure 8.6. Longitudinal deterioration in category fluency over one year for individual DAT patients, expressed as Z-scores (minimal DAT: open boxes, mild DAT: closed boxes)



Discussion

Use of neuropsychology in staging DAT

Before discussing the results of the longitudinal analysis, it is worth recapitulating the findings of the previous cross-sectional studies which confirmed the previous finding of severely impaired anterograde episodic memory, even in the minimal subgroup, with deficits in virtually all components of remote memory and semantic memory in both patient groups. By contrast, working memory was preserved in the minimally affected subgroup. This pseudo-longitudinal comparison suggests a consistent pattern of progressive impairment of subcomponents of memory. In the very early stages, delayed recall becomes impaired, with relatively early but less profound involvement of remote and semantic memory. That working memory is involved only in more established disease fits with current knowledge regarding the anatomical spread of DAT pathology [42], the frontal lobes being relatively spared by DAT pathology until later in the disease.

For the minimal group, only famous face and famous name identification showed a significant decline over one year. This is interesting given what is known about the neural substrate for anterograde and remote memory. While anterograde amnesia can occur with hippocampal, particularly transentorhinal, pathology, retrograde amnesia occurs when pathology extends outwith this region. My finding of remote memory impairment may thus be due to extension of pathology from the transentorhinal to other temporal lobe structures.

There was surprisingly no longitudinal deterioration in any of the working memory tests in the mild DAT subgroup. This is at variance with the study by Baddeley *et al* [14] who found a deterioration over one year using a similar test. It may be that the decline in working memory has failed to reach significance due to the considerable variation in the mild DAT patients' performance at year 1. Of the anterograde tasks, there was evidence of a further deterioration in immediate recall, but no further decline in delayed recall, suggestive of a floor effect. Remote memory continued to decline significantly. It is notable that there was a significant decline on the personal semantic component of the AMI and famous face and name identification, consistent with a loss of semantic knowledge regarding both autobiographical memory and memory for famous persons. This is in keeping with the concept of semantic breakdown occurring early in the course of DAT [143, 149]. Of the general semantic memory tests, however, only category fluency showed a significant decline over one year.

In summary, my longitudinal study indicates that anterograde episodic memory is the first subcomponent of explicit memory to become impaired in early DAT, followed by subsequent impairment of remote and semantic memory in more

established disease. This is in accord with neuropathological studies of progression of DAT [42] as discussed early (see Chapter 1), and current brain-behaviour relationships of subcomponents of memory [257].

Summary

I administered tests of the following subcomponents of memory to 24 DAT patients longitudinally at a one year interval. The results indicated that minimal DAT patients showed further impairment of remote memory for famous figures. Mild DAT patients showed further deterioration in immediate recall, remote memory and semantic memory. These longitudinal data confirm and extend existing theories derived from cross-sectional studies regarding the use of subcomponents of memory in both diagnosis and staging DAT.

Chapter Nine

The fractionation of remote memory: Evidence from a longitudinal study of dementia of Alzheimer type

Introduction

The work described in the Chapter builds upon the earlier cross-sectional study of remote memory for famous people (see Chapter 3) and of autobiographical memory (see Chapter 5). The two principal issues addressed here are the fractionation of remote memory and the nature of the remote memory deficit in DAT in terms of contemporary cognitive models.

One broad subdivision of remote memory proposed by a number of workers is that between memory for personal life events (autobiographical memory) and memory for public figures and events. Several case studies have shown deficits restricted to public figures or events [87, 101, 103], or to autobiographical memory [79, 141, 319]. Within the domain of autobiographical memory, a subdivision has been proposed between memory for personal semantics and incidents [190]. In support of this proposal, relatively selective deficits of either incident memory [79, 141, 216] or personal semantic memory [87, 144, 344] have been described.

These findings raise theoretical issues regarding the nature of autobiographical memory [142]. To summarise Chapter 5, it has been suggested that autobiographical memory has a different representation and/or organisation than memory for public events [12]. Retrieval and remembering autobiographical memories are thought to involve a complex, distributed system which requires problem solving, cross checking, verification and inference [12, 69]. Loss of autobiographical memory may be due either to disruption of so-called thematic retrieval frameworks or a loss of individual memory traces, as can occur in damage to fairly widely distributed temporo-parietal cortices [172, 173, 208]. For general semantic knowledge, the left temporal neocortex is felt to play a critical role [256]. The issue of whether knowledge about famous people is represented in areas closely related to those specialised for face recognition - the infero-medial right temporal lobe - remains controversial, but all three cases so far reported with loss of person-specific semantic knowledge have had right temporal lobe pathology [101, 103, 128].

Studies involving famous faces [25, 148, 360] and famous events [188, 280] have all shown remote memory impairment in DAT. Hodges *et al* [148] borrowed techniques from cognitive neuropsychology to address the nature of the remote memory impairment seen in DAT. They took the information-processing model of face identification proposed by Bruce and Young [47], and amended by Valentine *et al* [333] to include name processing.

These serial models which were described in Chapter 3 have been modified to an interactive activation and competition architecture (IAC) model for face and name recognition [46, 53, 54] and naming of faces [52] which share in common with more

traditional models the principle that naming occurs only if semantic information is present.

My own study builds upon previous work by Hodges *et al* [148] who analysed recognition of famous faces from amongst non-famous foils, identification (i.e. the ability to provide specific information about un-named faces) and naming, with and without semantic and phonological (first name) cues. Their DAT group was impaired on all components, but showed relative preservation of recognition, and naming with first name cues. They argued that the impairment was due primarily to loss of person-specific semantic knowledge and that pre- and post-semantic processes remain relatively spared in DAT. As stated in Chapter 3, I found evidence of impairment on all components of remote memory, with a gentle temporal gradient. Again, the bulk of the deficit was at the level of semantic processing.

Autobiographical memory, despite its obvious everyday importance, has been investigated relatively little in DAT, perhaps due to the unavailability, until recently, of suitable instruments. Sagar *et al* [280] gave the cued autobiographical test [modified from Crovitz and Schiffman [73]] and showed impaired autobiographical memory, with a shift in the pattern of responses to more distant time periods. Kopelman [188] found that both the personal semantic and episodic components of autobiographical memory were impaired, with a modest temporal gradient. Impaired autobiographical memory was also noted by Dall'Ora *et al* [78], although they did not find a temporal gradient. My cross-sectional study (see Chapter 3) confirmed that autobiographical memory was impaired in DAT, even in patients with minimal disease, and that there was evidence of a very mild temporal gradient on only one of four measures; personal incident memory on the AMI. There was, therefore, some support for the fractionation of autobiographical memory into personal semantic and incident components.

The major limitation of all of the above studies of remote memory relates to their cross-sectional design. Although such methods are adequate for testing anterograde episodic memory, where the examiner can control and verify the presentation of material to be learned, there are significant drawbacks in studies of remote memory. In studies involving famous people (or events), failure to identify or name the target famous figure may represent a loss of knowledge of the famous person; alternatively, the subject may have never known the identity of the famous person in the first place. Differences in education and attention paid to current affairs lead to subjects having widely varying premorbid databases regarding public figures and events. For instance, a DAT patient's inability to recognise, identify and name Groucho Marx may be due to loss of semantic knowledge of him. Alternatively, the subject may have never watched much television or gone to the cinema, and may never

have known who Groucho Marx was. Attempts to match patients and controls on the basis of age, education and baseline IQ do not totally deal with this problem.

A further problem with studies of autobiographical memory relates to checking the veracity of subjects' responses, which may be confabulations. This can be controlled for either by retesting the patients after an interval, or by verifying the results with family members, both of which are time-consuming and not entirely reliable. Another complicating factor is that some people have intrinsically less eventful lives, and this may result in poorer performance on autobiographical tests.

In longitudinal studies, patients act as their own controls, which allows one to circumvent many of these drawbacks. This is particularly advantageous when trying to determine the nature of the cognitive deficit underlying remote memory impairment. For instance, if a patient can identify Groucho Marx at year 1, then we know that he forms part of the subject's database regarding famous people. Failure to do so a year later may be due to a loss of storage of semantic knowledge regarding Groucho Marx, or alternatively due to an inability to retrieve this information. Retrieval deficits would also, however, be as likely to lead to misidentification at year 1 and correct identification at year 2. By adjusting for this, I hope to study how much any apparent deterioration in identification longitudinally may be occurring as a result of loss of semantic knowledge storage, and how much might be due to retrieval deficits. This is of theoretical importance given the debate regarding whether the general semantic impairment seen in DAT is primarily one of loss of storage, or lack of access due to a retrieval deficit. Although the bulk of investigators favour the former explanation [65-67, 149, 213], others favour an access deficit [22, 242].

To the best of my knowledge, there have been no reported longitudinal studies of remote memory in DAT. My study was undertaken to examine the relationship between remote memory for public figures and autobiographical memory in a group of patients with early DAT. The finding of decline in only one putative subcomponent of remote memory would argue powerfully for the proposed fractionation of remote memory.

Aims

I wished to address the following questions:

1. Is there evidence of deterioration of remote memory over one year in DAT patients, as measured by both autobiographical memory and person-specific memory for famous people ?

2. Within the realm of remote memory, is there any support for the proposed fractionation between autobiographical memory and memory for famous people ?

3. If there is a deterioration in public memory, which aspects of face and name processing appear responsible ?
4. If there is decline in ability to identify and name famous people, is this due to a loss of storage of semantic information, or due to a failure of access ?

Methods

Subject group

Two groups consisting of a total of 54 subjects participated in the study: 24 patients with DAT (15 females and 9 males) and 30 neurologically intact normal control subjects (15 females and 15 males). These were the same patients described in Chapter 8. Written informed consent was obtained from all subjects or the caregivers, where appropriate.

Table 9.1. Mean (S.D.) age, education and MMSE scores for the DAT cases and normal control subjects

	Controls n=30	DAT patients n=24
Age	67.9 (8.7)	69.8 (8.6)
Education (yrs)	11.0 (2.9)	11.3 (3.1)
IQ (NART)	114 (7.8)	113 (9.5)
MMSE score	29.5 (0.7)	23.9 (4.1)*
Range	(26-30)	(17-30)
Logical Memory - Immediate	19.8 (5.6)	8.3 (4.4)*
Logical Memory - Delayed	17.6 (6.0)	2.3 (3.4)*
Category fluency	112 (23.6)	64 (20.5)*

Key

* $p<0.0001$

The DAT subjects were followed up one year later, when the autobiographical and famous faces and famous names tests were repeated. For each patient, and for each face, longitudinal performance could be determined on each of the following measures: face recognition, identification and naming, and name recognition and identification. Five of the controls were retested. There was no significant difference on any of the remote memory tests over one year. Thus any change with time on the memory tests in the DAT subjects is likely to be attributable to DAT pathology rather than ageing over one year.

Statistical analysis

For analysis of the autobiographical and public memory tests, inter-group differences between DAT patients and controls were tested using unpaired comparisons. Performance on these tests longitudinally was studied by paired comparisons.

To study the relationship between public and autobiographical memory within remote memory, a correlational analysis was performed. On account of the number of comparisons, only those correlations with a p-value less than 0.01 were considered significant.

The issue of the relationship between public and autobiographical memory for the DAT subjects was further addressed by entering public and autobiographical test results into a principal components factor analysis using a Varimax rotation on the entire data set. Only those factors with eigenvalues above 0.5 were reported.

Longitudinal performance on remote memory was assessed for each subject. For each famous face, it was possible to study performance with time for each of the following measures: face recognition, face identification, face naming, name recognition and name identification. For example, for recognition of a particular face, the subject's performance at year 1 and year 2 were determined. Fifty items for each of 24 patients yielded 1200 subject-faces. To study item-by-item correspondence on tests of subcomponents of public memory, contingency tables using Chi square were used. Admittedly, there are statistical reservations about using such a contingency analysis, as each datum should be independent of each other. My data are related, either by fifty such data being done by one patient, or alternatively by referring to performance on a particular famous figure. I thus draw conclusions from my contingency tables with caution.

Results

Cross-sectional study of memory for famous people and autobiographical memory

My cross-sectional data comparing DAT patients and controls are presented in Chapters 3 and 5 and will be summarised only briefly. For memory for public figures, I found that all components of the faces (recognition, identification, naming) and names (recognition, identification) tests were impaired in DAT patients with disproportionately severe deficits in identification (see Table 9.2). Similarly, for autobiographical memory, DAT patients were significantly impaired with respect to controls, on both the Autobiographical Memory Interview and autobiographical fluency tests (see Table 9.2).

Table 9.2. Longitudinal neuropsychological test data for DAT patients at year 1 and year 2, and for controls (with standard deviations), with significance levels (p-values)

		Controls *(n=30)*	DAT (year 1)† *(n=24)*	DAT (year 2)† *(n=24)*
Public	FF recognition	43.0 (6.7)	37.2 (10.1)*	39.8 (9.7)
	FF identification	39.3 (8.8)	25.5 (10.6)***	21.5 (11.0)***
	FF naming	31.0 (9.1)	10.4 (7.4)***	9.4 (7.8)
	FN recognition	49.7 (0.7)	48.0 (2.7)**	47.1 (3.2)
	FN identification	49.1 (1.3)	40.4 (6.1)***	32.1 (9.0)***
ABM	AMI - personal semantic	60.0 (3.5)	45.0 (10.8)***	42.0 (10.7)*
	AMI - incident	21.7 (5.0)	11.1 (6.6)***	10.4 (6.6)
	ABF - names	26.8 (10.9)	8.7 (5.4)***	7.6 (5.0)
	ABF - events	16.5 (7.0)	6.4 (5.0)***	6.1 (4.1)

Key

* $p<0.05$ ** $p<0.01$ *** $p<0.001$

† Significance levels at year 1 refer to difference between DAT patients and controls (unpaired comparisons). Levels at year 2 refer to difference between patients at years 1 and 2 (paired comparisons).

ABM Autobiographical memory

FF Famous face

FN Famous name

AMI Autobiographical memory interview

ABF Autobiographical fluency

To study the issue of the fractionation of remote memory, results of my tests of public and autobiographical memory were entered into a correlation analysis (see Table 9.3). It can be seen that there were no significant correlations between any of the tests of public memory and any of the autobiographical memory tests. This suggests that public and autobiographical memory are indeed separate subdivisions within remote memory.

Table 9.3. Correlation between autobiographical memory and memory for public figures in DAT patients

	FFR	FFI	FFN	FNR	FNI	AMI-pscm	AMI-incident	ABF names	ABF events
FFR	1.00								
FFI	**0.81****	1.00							
FFN	**0.54****	**0.77****	1.00						
FNR	0.17	0.40	0.30	1.00					
FNI	0.40	0.65**	0.49*	0.79**	1.00				
AMI-pscm	0.09	-0.03	0.04	-0.09	0.14	1.00			
AMI-incident	0.21	0.22	0.28	0.17	0.36	**0.55****	1.00		
ABF names	0.08	0.03	0.03	-0.06	0.13	**0.69****	0.32	1.00	
ABF events	0.11	0.18	0.03	0.21	0.39	0.41	**0.59****	0.44*	1.00

Key

FFR	Famous face recognition
FFI	Famous face identification
FFN	Famous face naming
FNR	Famous name recognition
FNI	Famous name identification
AMI-pscm	Autobiographical Memory Interview - personal semantic
AMI-incident	Autobiographical Memory Interview - incident
ABF names	Autobiographical fluency for names
ABF events	Autobiographical fluency for events
*	p<0.01
* *	p<0.001

An alternative means of addressing this issue is to enter the tests of public and autobiographical memory into a principal components analysis. As performance on face recognition influences identification and subsequent naming, only face identification was entered into the factor analysis. Similarly, only the identification component of the famous names test was entered.

As can be seen from Table 9.4, three separate factors emerged. One comprised the names component of the autobiographical fluency test and the personal semantic component of the AMI: this factor seems to represent personal semantic memory. The second factor comprised famous face and name identification, i.e. a measure of knowledge regarding famous persons, whether accessed by faces or names. The third factor, the events component of autobiographical fluency and the incident component of the AMI, represents incident-related episodic autobiographical memory. This again argues that the subdivision of remote into public and autobiographical memory is

indeed relevant. In addition, it supports the fractionation of autobiographical memory into personal semantic and incident memory.

Table 9.4. Summary of loadings for public and autobiographical memory in DAT patients after principal components factor analysis

	Factor 1	Factor 2	Factor 3
Famous face identification		0.91	
Famous name identification		0.78	
AMI - personal semantic	0.68		
AMI - incident			0.75
ABF - names	0.87		
ABF - events			0.67

AMI Autobiographical memory interview

ABF Autobiographical fluency

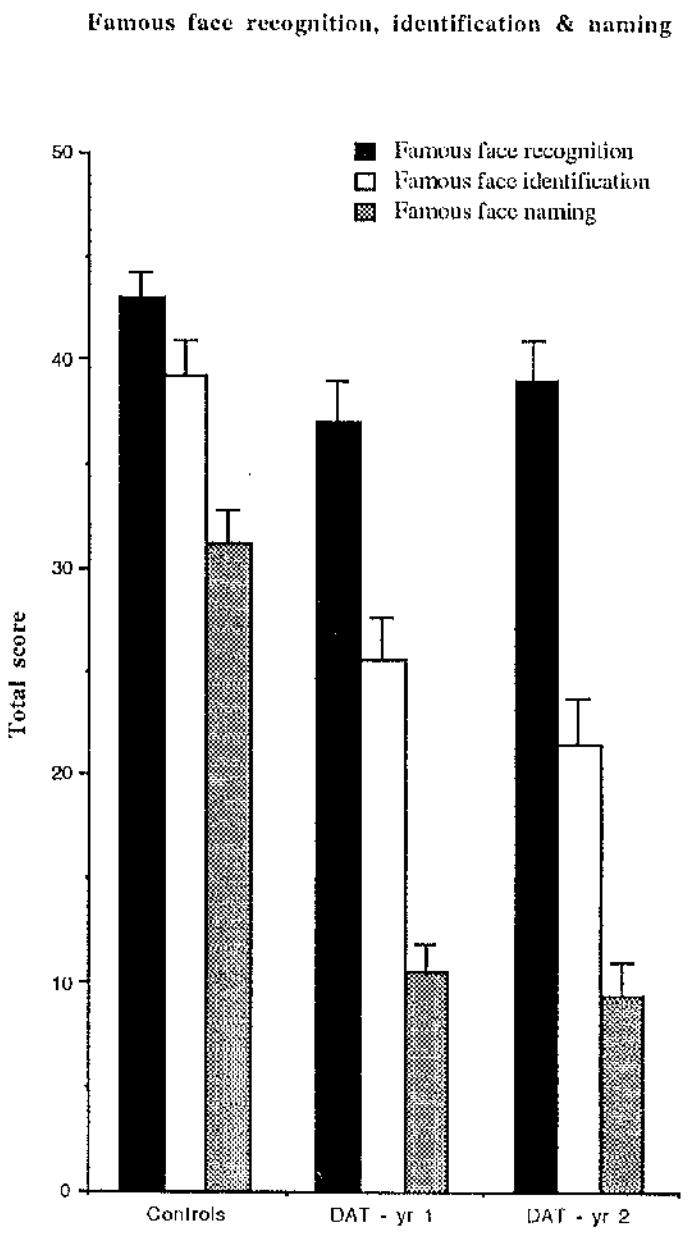
Longitudinal study of memory for famous people and autobiographical memory

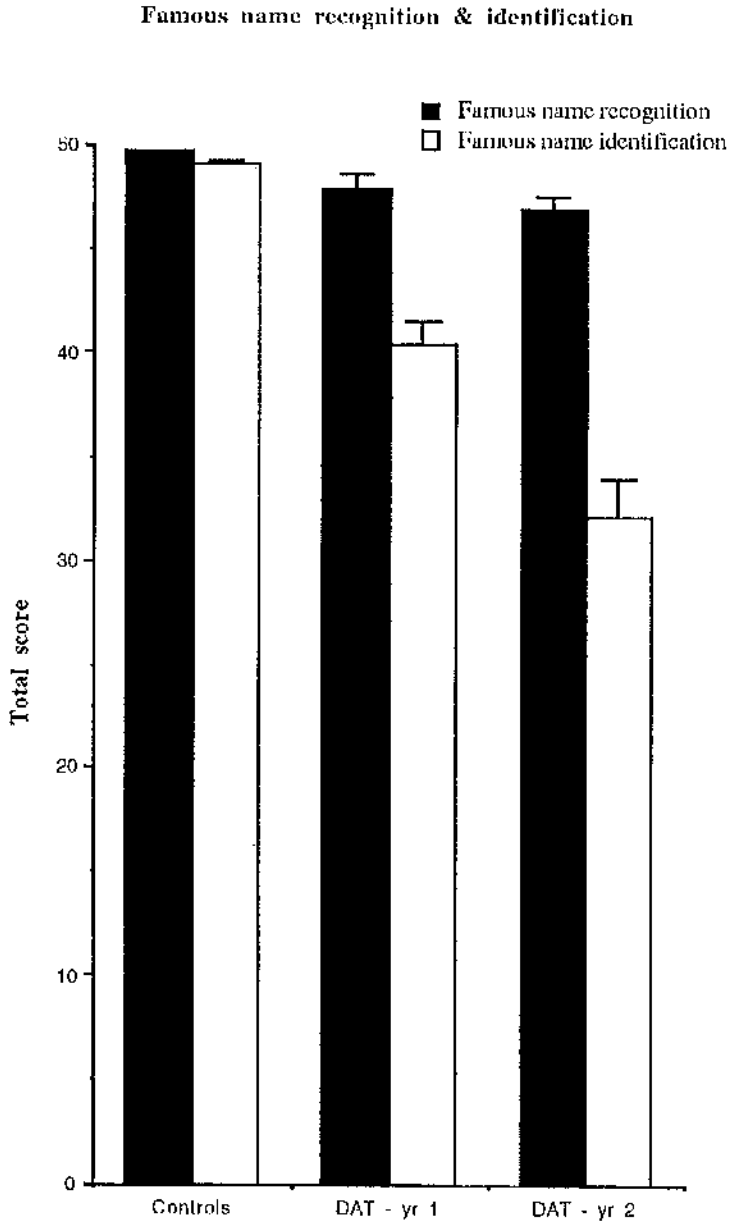
Cognitive analysis of remote memory for public figures

To study the impact of disease progression on subcomponents of face processing, I performed a two (groups: DAT yr 1 vs. DAT yr 2) by three (conditions: recognition, identification, naming) ANOVA which indicated a non-significant effect of group ($F(1,46)=0.1$, $p>0.05$), a significant effect of condition ($F(2,92)=379$, $p<0.0001$) and a significant interaction ($F(2,92)=5.3$, $p<0.01$). Post hoc pairwise comparisons show that this was due to a longitudinal deterioration in performance on identification ($p<0.001$), but not recognition or naming (both $p>0.05$) (see Table 9.2 and Figure 9.1).

A similar analysis for famous names revealed an effect for group ($F(1,46)=10.2$, $p<0.01$), condition (recognition, identification) ($F(1,46)=172$, $p<0.0001$) and a group by condition interaction ($F(1,46)=18.2$, $p<0.0001$). Post hoc pairwise comparisons showed that this was a result of DAT patients deteriorating significantly on famous name identification over one year, but not on name recognition.

Figure 9.1. Performance on public memory (famous face recognition, identification and naming, and famous name recognition and identification) by DAT patients at years 1 and 2 and controls (with standard errors shown)





At a cognitive level, the longitudinal deterioration in identification of faces and names is consistent with a breakdown in central semantic knowledge regarding famous figures. The relative preservation of face and name recognition, and face naming, argues that face and name recognition units, and the post-semantic lexicon were not further impaired by DAT in the year of study.

A more sophisticated means of analysing my longitudinal data at a cognitive level is by adopting an item-by-item approach; I can compare each patient's performance for each famous face longitudinally, which lets me circumvent the problem of not being sure of the extent of subjects' premorbid knowledge of famous people which bedevils studies of remote memory.

Contingency tables for longitudinal results of each of the components of face and name processing are shown in Table 9.5. The recognition tasks were excluded since these employed a forced choice recognition paradigm. As forced choice introduces the possibility of guessing, I felt that I could not draw firm conclusions from my longitudinal study of recognition. Identification and naming did not involve a forced-choice paradigm.

For famous face identification, overall performance fell from 544 to 379 patient-faces over a year, a drop of 165. It can be seen that there were, however, 208 instances of a face being correctly identified at year 1 and wrongly identified at year 2. These 208 instances may be due to loss of storage of semantic knowledge regarding this famous person, or alternatively may simply be due to a retrieval deficit. In the opposite circumstance, where the subject cannot identify the famous person at year 1, but can do so at year 2, then clearly the storage system is intact, and the impaired performance at year 1 must simply have been due to a retrieval deficit. It is reasonable to assume that retrieval deficits are as likely to cause impaired identification at year 1 (but not year 2), as they are to cause impaired identification at year 2 (but not year 1). Thus, in a crude manner, we can try to allow for the effect of retrieval deficits to produce a measure of how much of the longitudinal deterioration in knowledge of famous persons is genuinely due to loss of semantic information. There were 43 instances of wrong identification at year 1 but correct identification at year 2. We can assume that these improved responses are due to retrieval errors at year 1, and not to loss of knowledge. To control for retrieval deficits contributing to correct score at year 1 but incorrect identification at year 2, we can subtract 43 cases from the 208, leaving 165 cases of loss of identification over a year which are likely to be due to loss of semantic knowledge of the famous face. The ratio of retrieval deficits in year 1 to loss of information from year 1 to 2 was, therefore, 43:165, or approximately 1:4. Although by no means conclusive, my data suggest that the deterioration in semantic knowledge regarding famous people is primarily due to a loss of storage rather than a deficit in access.

The deterioration in famous face naming was less marked than for identification. Overall, naming fell from 245 correct on year 1 to 224 on year 2, a drop of 21. There were 105 instances of loss of correct naming over one year, but 84 with the opposite effect. Thus face naming shows significant retrieval deficits at years 1

and 2. There was, however, little evidence of a significant deterioration in face naming over the year.

Table 9.5. Performance by DAT patients on face recognition, identification and naming, and name identification at year 1 and 2

Face identification

		Year 1: 0	Year 1: 1	
Year 2	0	613	208	821
	1	43	336	379
		656	544	1200

Face naming

		Year 1: 0	Year 1: 1	
Year 2	0	871	105	976
	1	84	140	224
		955	245	1200

Name identification

		Year 1: 0	Year 1: 1	
Year 2	0	251	344	595
	1	28	577	605
		279	921	1200

My findings on the identification component of the faces test were largely mirrored by performance on famous names. Famous name identification fell from 921 correct responses on year 1 to 605 on year 2, a fall of 316. The total number of responses changing from correct to incorrect was 344, with only 28 changes in the opposite direction: a ration of 28:344, i.e. around 1:10. This would suggest that the deterioration in famous name identification over year could be attributed largely to loss of storage of famous names rather than to retrieval deficits.

I was puzzled by the deterioration in face identification but not naming, given that naming is dependent on semantics. I postulate that cases showing longitudinal deterioration in identification may have had impaired naming in the first instance. I analysed, therefore, naming in all instances where identification had declined over 1 year. Unpaired comparisons confirmed that, in those subject-faces where face identification became impaired over one year, there were significantly more instances

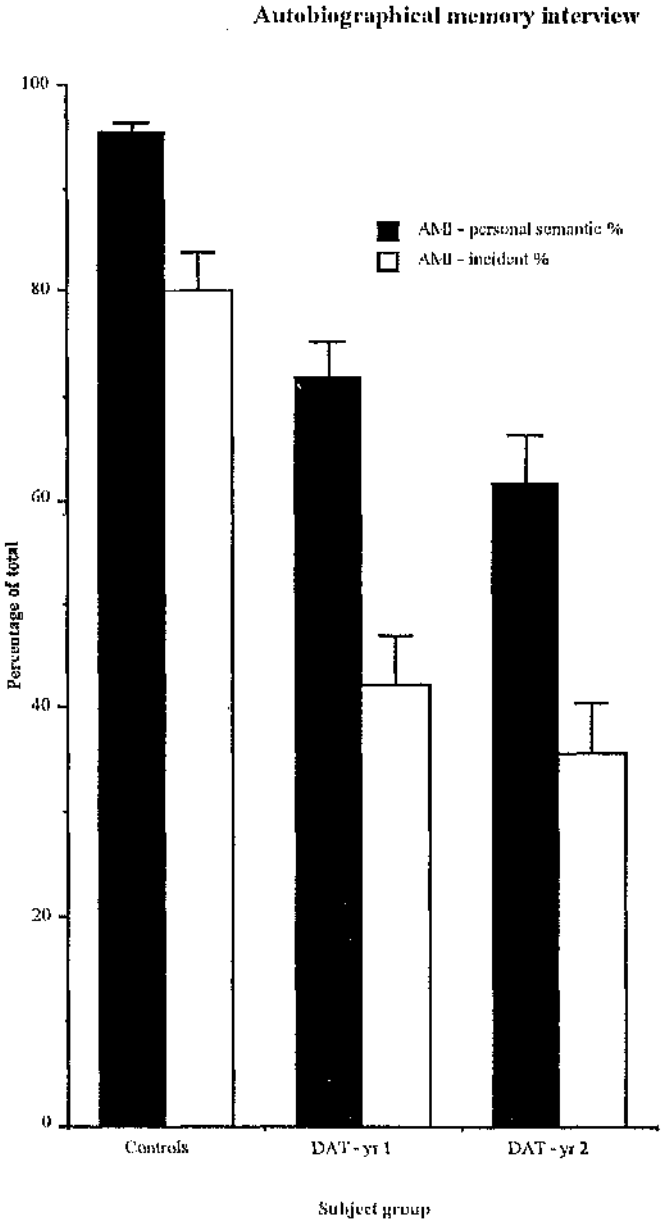
of initially impaired naming of the same face than of intact naming ($t=2.98$, $p<0.01$). This at least partly explains the somewhat anomalous finding of longitudinal deterioration in identification but not naming, without having to postulate the existence of naming without semantics [192, 193, 298].

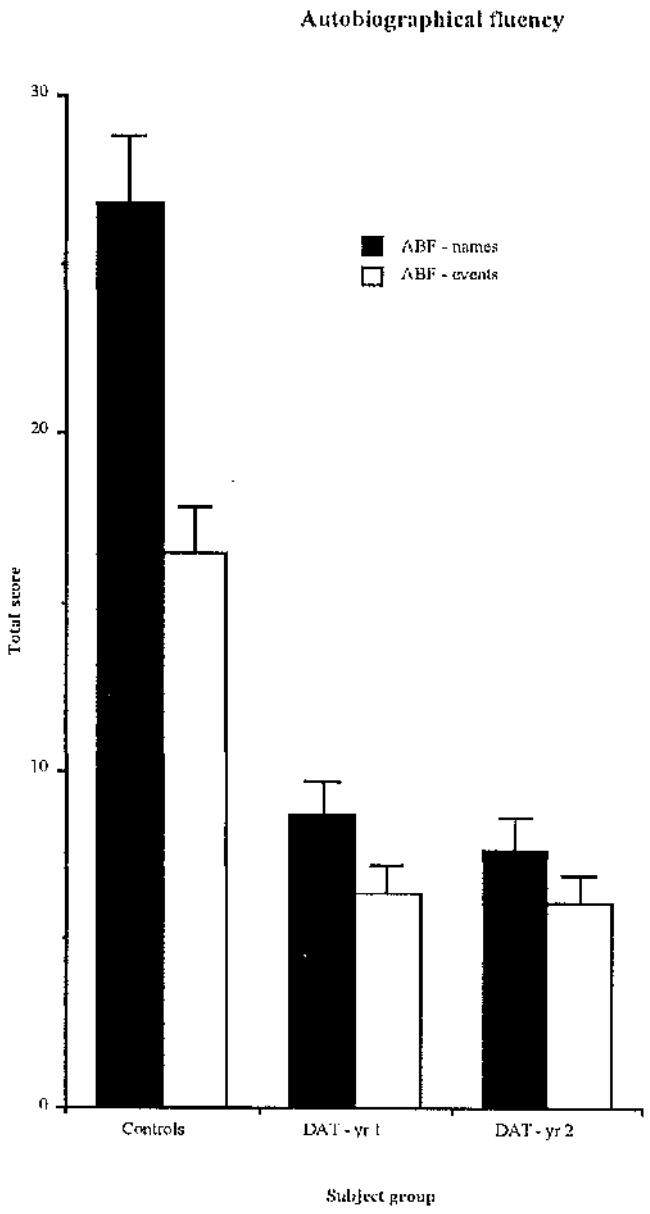
Fractionation of remote memory

The co-administration of tests of public and autobiographical memory allowed me to address the issue of the fractionation of remote memory over time.

To summarise findings on autobiographical memory, paired comparisons of performance at years 1 and 2 on tests of autobiographical memory showed no deterioration on any of the autobiographical tests ($p>0.05$) (see Table 9.2 and Figure 9.2). This lack of deterioration is in contrast with that noted above for public memory, and is further evidence that these subcomponents of remote memory are dissociable.

Figure 9.2. Performance on autobiographical memory (personal semantic and incident components of the Autobiographical Memory Interview, and names and events components of autobiographical fluency) by DAT patients at years 1 and 2 and controls (with standard errors shown). Results for AMI have been expressed as percentages as the personal semantic and incident components have different maximum scores (63 and 27 respectively).




Autobiographical fluency
30
20
10
0
Total score
ABF - names
ABF - events
Controls
DAT - yr 1
DAT - yr 2
Subject group

Another means of addressing the relationship between public and autobiographical memory is to ascertain the percentage change over one year for the various subtests. If public and autobiographical memory were not dissociable, then I would expect deterioration in public memory to be invariably accompanied by a similar deterioration in autobiographical memory. Table 9.6 shows that such a relationship was not observed; the percentage change in famous face identification correlated significantly with the percentage change in the incident component of the AMI, but no other relevant correlations were found.

Table 9.6. Correlation matrix based on % change in public and autobiographical memory over one year in DAT patients

	FFR%	FFI%	FFN%	FNR%	FNI%	AMI pcem%	AMI incident%	ABF names%	ABF events%
FFR%	1.00								
FFI%	0.32	1.00							
FFN%	0.21	0.75**	1.00						
FNR%	-0.15	0.31	0.26	1.00					
FNI%	-0.02	0.63*	0.41	0.68**	1.00				
AMI pcem%	0.23	0.40	0.34	0.06	0.24	1.00			
AMI incident%	0.34	0.59*	0.46	0.13	0.12	0.39	1.00		
ABF names%	-0.13	0.36	0.28	0.31	0.36	0.47	0.09	1.00	
ABF events%	0.25	0.24	0.03	0.16	0.03	0.02	0.39	0.73	1.00

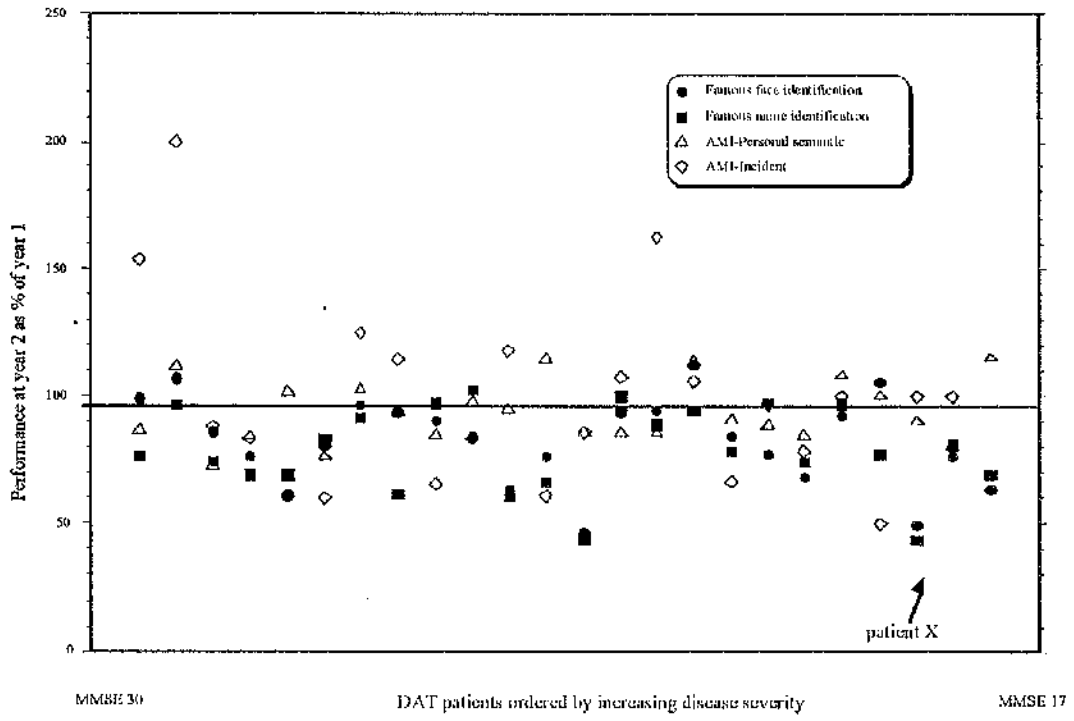
Key	% change in:
FFR%	Famous face recognition
FFI%	Famous face identification
FFN%	Famous face naming
FNR%	Famous name recognition
FNI%	Famous name identification
AMI pcem%	AMI - personal semantic
AMI incident%	AMI - incident
ABF names%	Autobiographical fluency - names
ABF events%	Autobiographical fluency - events

Key
* $p<0.01$
** $p<0.001$

Finally, my group data may be complemented by a multiple single case approach. Figure 9.3 illustrates the percentage change in public and autobiographical memory tests over one year. Each column represents a single patient; the patients have been ordered by disease severity as defined by the MMSE score at year 1. For clarity, only the identification components of the faces and names tests, and the more established of the autobiographical tests (the AMI) are shown. It can be seen that the percentage change in public memory performance is not always mirrored by percentage change in autobiographical memory. For example, patient X shows a much greater deterioration in public memory than autobiographical memory. None of my patients, however, showed the opposite pattern, that is to say a markedly more profound deterioration in autobiographical memory than the accompanying deterioration in public memory. My results are in keeping with the separability of public and autobiographical memory. By failing to provide evidence of a patient with

clear-cut evidence of a longitudinal deterioration in autobiographical but not public memory, I have fallen short of showing the double dissociation that would argue strongly for the separability of these subcomponents of remote memory. Nevertheless, my results illustrate that deterioration in public memory and autobiographical memory are not invariably linked.

Figure 9.3. Univariate scattergram of performance by the DAT patients at year 2 expressed as a percentage of their performance at year 1 on tests of public and autobiographical memory, ordered by increasing dementia severity (as determined by MMSE).



Discussion

Studies of remote memory have been plagued with methodological difficulties, primarily due to difficulty in ascertaining the premorbid databases of autobiography and knowledge of public figures and events once carried by the DAT subjects. By extending my cross-sectional study of remote memory in DAT longitudinally, thereby using the patients as their own controls, I have attempted to overcome such difficulties. My inquiry has focused on two issues in particular: the fractionation of remote memory, and a cognitive analysis of the nature of the remote memory deficit.

In summary, I have confirmed that autobiographical and public memory are both impaired in DAT. There was evidence of longitudinal deterioration in public memory but not autobiographical memory, supporting the fractionation of remote

memory into autobiographical memory and memory for famous people. At a cognitive level, the deterioration in public memory was due to impairment at the level of famous face and name identification, and to famous face naming. The loss of identification appeared to be due to loss of storage of semantic information, whereas the impaired retrieval contributed to the naming deficit. I shall now address these points in more detail.

Fractionation of remote memory

My cross-sectional data confirm previous work showing that both public and autobiographical memory are impaired in DAT [78, 148, 188, 280]. I have extended this and found evidence of longitudinal deterioration in famous face and name identification, but no such deterioration for autobiographical memory. These findings are in keeping with the growing number of single-case reports highlighting the separability of public and autobiographical memory. This implies that these two domains of remote memory are functionally, and presumably anatomically, distinct.

One potential reason for an apparent dissociation between autobiographical and public memory might be the occurrence of so-called "floor effects" on one (or other) task; in other words, if autobiographical memory were already very impaired at the time of presentation, there might theoretically be no further room for deterioration. Although the patient group showed substantial deficits in autobiographical memory, it can be seen from Figure 9.2 that their performance was clearly above floor, with scope for further decline. The differential decline appears, therefore, to be a real rather than artefactual finding.

The process of retrieving autobiographical memories requires problem solving, checking and verification, and depends upon so-called thematic retrieval frameworks [70, 141]. Autobiographical memories are multi-faceted with visual, verbal and other components: except in the case of over-rehearsed and flashbulb memories, their evocation is an active process which almost certainly requires the participation of frontal systems acting on widely distributed areas of posterior temporo-parietal cortex. This clearly differs in representation and organisation from memory for public figures [12]. Recalling information about a famous person from their name or face is a less re-creative process and appears to be relatively independent of frontal executive function [142]. Memory for public figures appears to rely on right temporal structures [101, 103, 128]. My finding of deterioration in public, but not autobiographical, memory is in keeping with this broad subdivision of remote memory.

Cognitive analysis of face and name processing: Storage vs. access

Turning now to the cognitive analysis of famous face and name processing, my results indicate that the bulk of the deterioration over one year in DAT is at the identification stage. By contrast, the same patients' ability to recognise faces and names from among closely matched foils did not decline. When interpreted in the context of the cognitive models of face and name processing outlined in Chapter 3 [47, 333], these findings suggest that there has been a progressive deterioration in semantic knowledge of famous people accessed from face or name, but with no deterioration in face or name recognition units. The finding that semantic knowledge, whether accessed by face or name, decline in parallel, suggests that face-derived and name-derived identification are drawing on the same store of semantic knowledge of the public figures.

If naming is dependent on semantic knowledge, as I have argued above, it is surprising that the deterioration in identification was not accompanied by a similar deterioration in naming. One might plausibly explain this finding as discussed in the Results section; the fact that naming was usually already impaired at year 1 in those instances where longitudinal deterioration occurred. This would explain my findings without invoking the existence of naming without semantics [192, 193, 298].

Some researchers have claimed that the deficits found on tests of general semantic memory in DAT may primarily reflect impaired access (for review see [22, 242]), but the majority of investigators support the explanation which hypothesises a breakdown in the structure of semantic memory [65, 66, 149, 213]. For instance, in both the studies by Chertkow and colleagues [66, 67] and that by Hodges *et al* [149] there was a highly significant item-by-item correspondence between DAT subjects' performance on picture naming and on other tests designed specifically to probe for semantic knowledge about the same items. This is, however, a controversial topic since item-by-item consistency, previously taken as evidence for a storage problem, may also result from impaired access [115], thus muddying the storage vs. access issue [263]. Although there was evidence that a retrieval deficit made a minor contribution to the identification impairment in my study, the bulk of the semantic impairment for face and name identification appeared to be due to loss of knowledge, in keeping with previous studies of remote memory in DAT [148].

It is interesting, however, that there was considerably more variability from year 1 to year 2 on the naming component of the faces test: overall performance fell by 21 person-faces but there were 105 instances of change from correct to incorrect over 12 months and 84 instances of change in the opposite direction. Thus, it would appear that although decline in identification represents a genuine loss of information (once patients are unable to describe the person, the deficit remains), impaired retrieval contributes significantly to the anomia. This finding goes some way towards

explaining the controversy over the issue of storage vs. retrieval loss in DAT: both are important but they contribute differentially to the semantic deficit and the name retrieval disorder for famous faces.

Summary

I studied remote memory, both autobiographical and public, longitudinally over a one year period in 24 patients with dementia of Alzheimer type (DAT). Although both public and autobiographical memory were impaired in DAT, there was a dissociation between the longitudinal deterioration seen for memory of famous persons but not for autobiographical memory. These data support the hypothesis that remote memory may be fractionated and that one important dichotomy is autobiographical memory vs. famous person knowledge. A cognitive analysis of famous face and name processing showed evidence of progressive breakdown in the identification of famous faces and names, and naming famous faces, with preservation of face and name recognition. The declining performance on identification appeared to be due primarily to loss of semantic knowledge regarding famous persons, while a retrieval deficit contributed more significantly to the proper name anomia which was over and above the semantic deficit in DAT.

Chapter Ten

Conclusions

This thesis has studied primarily the neuropsychology of memory. Rather than address one issue, this thesis has studied several areas of research in the neuropsychology of memory in DAT which are currently controversial. Consequently the importance and relevance of each chapter will be dealt with separately.

Remote memory in DAT

How early in the course of DAT does remote memory impairment occur ?

Remote memory is of great practical importance as it involves knowledge of relatives and friends, work etc, as well as more general knowledge regarding famous persons and events. Hence remote memory impairment is clearly devastating. I found that DAT patients showed impairment on all components of famous person-based remote memory, viz. famous face recognition, identification and naming, and famous name recognition and identification. This was in keeping with established wisdom.

Is there a temporal gradient, and if so, how steep is it ?

There was evidence of a very mild temporal gradient superimposed upon quite marked impairment across all decades tested (1940s-1980s). Most previous studies have found a temporal gradient, although some have not. It can be said that the temporal gradient, although present, is very gentle, quite unlike the marked gradient seen in Korsakoff's syndrome. In the latter condition, a pure episodic amnesia occurs due to diencephalic damage, yet semantic memory is preserved. In DAT, a combined episodic-semantic disorder [143], it might be argued that impaired memory for recent events is due to episodic impairment, while more distant memories are affected because of the semantic memory impairment. The disproportionate involvement of the most recent time period may, however, be due to the insidious onset of the anterograde deficit.

What is the relationship between remote and anterograde episodic memory ?

My main findings, which have not been described previously by others, relate to the dissociability of remote memory from anterograde and general semantic memory. Many individual case reports have demonstrated isolated anterograde or retrograde amnesia. In this group study, in contrast to the uniform impairment of anterograde memory, there was considerable heterogeneity in remote memory performance, indicating that anterograde and retrograde memory are functionally dissociable, and implying that these subcomponents of memory are subserved by different anatomical structures. Anterograde episodic memory utilises medial temporal-lobe structures [308]. In the domain of remote memory, it is necessary to consider the likely site of memory storage and the processes required to retrieve such information [142]. For

famous-person based knowledge, the anterior right temporal lobe appears to be a critical region [101, 103, 128].

What is the relationship between person-specific remote memory and general semantic memory ?

The association between tests of person-specific semantic memory and general semantic memory was also poor. This implies that these aspects of memory are functionally, and presumably anatomically, separate. While general semantic memory impairment is seen in dominant temporal neocortical pathology [82, 256], it appears that person-based semantic knowledge may utilise non-dominant temporal neocortex [101, 103, 128].

What is the basis for the deficit in face and name processing in DAT ?

My study is the first to address remote memory of famous people both by photograph and by name: an item-by-item approach suggested that accessing information of famous persons either by photograph or by name draws upon a common pool of semantic knowledge regarding the person. At a cognitive level, all subcomponents of face and name processing models seemed impaired, with semantic knowledge appearing particularly impaired.

Naming without semantics

With regard to my Famous Faces Test, is there any evidence of naming without semantics, i.e. can any of the patients ever name a famous face and yet have no other identifying knowledge about the person ?

Cognitive analysis of the patients' performance on the Famous Faces Test revealed no examples of preserved naming in the absence of semantic identifying information. I have thus directly rebutted the notion of naming without semantics, as proposed by Kremin [192, 193] and Shuren [298]. My findings were thus in line with established thinking which requires that knowledge of a person and presumably an object must be accessed in order subsequently produce the name.

The role of frontal executive function in autobiographical memory in DAT

Is autobiographical memory impaired in DAT, and if so, at what stage ? Is there a temporal gradient ?

This study confirmed autobiographical memory impairment in DAT, in keeping with other studies [78, 91, 185, 188, 280]. I extended these studies by showing that even minimal DAT patients had impaired autobiographical memory.

Is executive function impaired in DAT, and if so, at what stage ?

Previous studies of executive function in DAT have shown impairment in established disease [14, 19]. I, like Sahakian *et al* [281], have found working memory as assessed

by two separate dual-performance tasks and letter fluency, to be spared in DAT patients with minimal disease.

Do my data support the contention that executive function is implicated in the retrieval of autobiographical memory ?

Is there evidence for the further fractionation of executive function and autobiographical memory ?

The association between executive function and autobiographical memory was complex. Executive dysfunction appeared to play a significant, though limited, role in the autobiographical memory impairment. The deficit underlying autobiographical memory impairment was due both to impaired retrieval processes, and to a loss of memory stores. The neural basis of very long-term personal memories is uncertain, but since such memories often involve multiple sensory domains, it is likely that widely distributed posterior association areas are involved [80-82]. There was also evidence of fractionation within both executive function and autobiographical memory.

The nature of the anterograde memory deficit in DAT

What are the relative contributions of encoding, storage and retrieval to the anterograde memory in DAT ?

Although anterograde episodic memory has been extensively studied in DAT, I further studied this using a newly developed test, the Doors and People Test, in addition to more established memory measures, which has the advantage of including parallel tests of verbal and visual memory with recall and recognition paradigms, matched for level of difficulty. I found that the anterograde episodic memory deficit was primarily due to poor encoding. The learning rate was also impaired, but there was no evidence of a significant retrieval deficit.

Anatomically, the hippocampus is implicated in encoding new information [308], while other medial temporal structures are used in retrieval. Our finding of impaired encoding in minimal DAT would be compatible with hippocampal pathology early in DAT, which is in keeping with the pathological studies of Braak and Braak [42].

Is the forgetting rate accelerated in DAT ?

Initial results were suggestive of greater forgetting in DAT. This may however have been due to the contribution of short-term memory to immediate but not delayed recall. More detailed analysis of the CERAD test allowed for the contribution of short-term memory to immediate recall. True forgetting (i.e. the deterioration from the long-term component of immediate recall to delayed recall) was not accelerated. This result was supported by the Doors and People Test.

Previous studies of forgetting have argued for normal [26, 187] or accelerated [130] forgetting in DAT. These studies have been plagued by differences in methodology between studies. Using two different tests, I have found forgetting to be normal in DAT.

The finding of normal forgetting rate has important practical implications. Intensive cognitive and behavioural therapy may attempt to help DAT patients relearn salient personal information such as names, addresses and telephone numbers. If the forgetting rate is increased, a critic might argue that such therapy is wasteful, as the information will be lost in any case. My finding of a normal forgetting curve suggests that repeated presentations of information to overcome encoding deficits are worthwhile, as, once learned, DAT patients will forget no more quickly than controls.

Is there evidence of material-specificity for memory in early DAT ?

There was limited evidence that DAT may preferentially impair verbal or visual memory, i.e. some evidence of material-specificity, but it is difficult to quantify the degree of material-specificity, as defining a significant visual-verbal discrepancy is subjective. The finding of material-specificity in early disease is in keeping with work by Becker *et al* [29]. Clinically, this highlights the need to test memory for both verbal and nonverbal material in a subject with suspected early DAT.

Verbal and visual memory rely primarily on the left and right hippocampi respectively [252]. My finding of a degree of material-specificity in minimal DAT is compatible with asymmetrical disease, which has been shown by functional imaging studies [119].

How useful are episodic memory measures in staging DAT ?

Episodic memory measures were found to be of little use in staging DAT. Only the immediate recall component of logical memory, and the nonverbal recall element of the Doors and People Test reliably differentiated between minimal and mild DAT patients. The lack of use of episodic memory measures in staging is likely to be due to floor effects. Staging is better achieved using neuropsychological measures other than memory, or alternatively other non-episodic aspects of memory. However, within episodic memory, very easy recognition measures may be of use in staging DAT, and are currently being devised [16].

The use of neuropsychology of memory and SPECT imaging in the diagnosis and staging of DAT

In DAT, it is important to make the diagnosis not only to give a prognosis, but also to allow patients to benefit from drug therapies, which are likely to work best in early disease. Measures of staging disease severity are also necessary, partly to anticipate suitable provision of care, but also to assess the efficacy of these therapies. There is

no definitive diagnostic test for DAT *in vivo*, and clinical criteria such as the NINCDS-ADRDA [219] are approximately 80-90% accurate. As a result, considerable research is being conducted into the efficacy of various investigative measures. Given the current financial limitations to the provision of health care, it is important to be able to demonstrate that expensive investigations are sensitive and specific. This study has assessed neuropsychology and SPECT.

How useful are neuropsychological tests of memory in diagnosing and staging DAT ?

This study has confirmed the use of neuropsychology in both the diagnosis and staging of DAT. Due to ceiling and floor effects, the subcomponents of memory of most use in diagnosis were of least use in staging disease progression, and vice versa. This is in accord with previous studies which found that certain neuropsychological measures can discriminate DAT and elderly controls with a high degree of certainty [316, 352]. It is generally held that tests of memory are of most use in the early diagnosis, while non-mnemonic aspects of cognition such as praxis, fluency and visuospatial and perceptual function are of greater use in staging. I found, however, that certain measures of memory, in particular working, remote and semantic memory, were of use in staging.

How useful is SPECT in diagnosing and staging DAT ?

Although recent studies have claimed high sensitivity and specificity in diagnosing DAT [129, 170], I found SPECT imaging of limited use in diagnosing and staging DAT. Although I do not claim that the scanning system used represents state-of-the-art imaging, the scanner employed in this study is however representative of the quality of SPECT scanning which might be found in the Nuclear Medicine department of a typical British teaching hospital.

Despite the many caveats regarding the methodological problems of directly comparing neuropsychology and SPECT, which I have included in the Discussion section of Chapter 7, I feel that neuropsychology is of use both in diagnosis and staging, while SPECT is of limited use in diagnosis and staging. Villa *et al* have found neuropsychology to be more specific and more accurate than SPECT in discriminating DAT patients [338]. Van Gool *et al* [334] found that SPECT did not contribute substantially to diagnostic accuracy in elderly mildly demented outpatients who had been diagnosed using current clinical diagnostic criteria, and did not recommend its use for clinical diagnostic purposes.

What does SPECT tell us about the pattern of spread of DAT ?

In contrast to the established view of temporo-parietal hypoperfusion being characteristic of DAT, this study found the pattern of rCBF to be much more heterogeneous than is usually described. One might argue that this was due to some of the subjects having non-AD pathology. The NINCDS-ADRDA criteria, used in this

study, have been shown to be at least 80% accurate in the diagnosis of AD, and I feel that the observed heterogeneity is not simply a result of possible misdiagnosis in some of the patient group. In any case, as the patients are enrolled in a longitudinal study and have agreed to post mortem, it will be possible to answer this criticism definitively in time.

It should be noted that areas of reduced rCBF do not necessarily equate with areas of pathology. It may be that hypoperfusion occurs in pathologically unaffected tissue which is secondarily deafferented from other areas of pathology. For instance, the temporo-parietal hypoperfusion classically described in DAT does not necessarily mean that there is temporo-parietal Alzheimer pathology, but may simply reflect perihippocampal Alzheimer pathology functionally deafferenting pathologically unaffected temporo-parietal cortex [167]. Thus, I can only say that the pattern of rCBF in DAT, and not necessarily the anatomical spread of AD pathology, is more heterogeneous than is classically stated. Obviously, when histological proof of AD pathology becomes available post mortem, I will be able to state with certainty whether or not the rCBF imaging described here is due to AD.

Longitudinal decline in memory in DAT

Which aspects of memory decline longitudinally in DAT patients with minimal and mild disease?

How do my longitudinal data contribute to the use of various components of memory in both diagnosing and staging DAT?

Results from my longitudinal study dove-tailed with my cross-sectional study. Follow-up of the minimal DAT group showed further impairment of remote memory. The mild group showed further deterioration in immediate recall, remote memory and semantic memory. The results confirmed and expanded findings from cross-sectional data regarding the use of subcomponents of memory in diagnosis and staging DAT. There was also evidence of considerable heterogeneity regarding the rate of decline in DAT [38].

These issues are currently being addressed by the Consortium to Establish a Registry for Alzheimer's disease. The strength of their study is that, being multi-centre, they are able to enrol large numbers of patients. This thesis cannot compete with their study for logistic reasons. It should be noted however that the neuropsychological battery being administered by the CERAD group is relatively superficial. I feel that the strength of this thesis relates not to the numbers of subjects, but to the depth of probing of cognitive function. This particularly applies to the longitudinal study of remote memory, which I shall now address.

Longitudinal study of remote memory in DAT

As mentioned in the Introduction, remote memory is particularly suitable for longitudinal study. To my knowledge, there has been no previous longitudinal study of remote memory in DAT.

Does memory for public figures and/or autobiographical memory deteriorate longitudinally in DAT ?

Is there support for the fractionation of remote memory for public and autobiographical facts ?

Longitudinal study revealed a deterioration in memory for public figures, but not in autobiographical memory. This dissociation between autobiographical and public memory is in support of the fractionation of remote memory.

If there is a deterioration in memory for public figures, which cognitive component of face processing is responsible ?

A cognitive analysis utilising current face and name models showed a longitudinal deterioration in identifying famous faces and names, and naming famous faces, but with no longitudinal deterioration in face and name recognition. This argues that face and name recognition units are relatively spared, and that the major impact of the disease is on person-specific semantic knowledge. This deterioration appears to be due to a loss of storage of semantic knowledge regarding the famous people, rather than a lack of access to such information [65, 149].

Criticisms

I feel that longitudinal studies remain a useful means of investigating a neurodegenerative disease such as Alzheimer's. Although it is desirable to test frequently enough to detect subtle changes, assessment at yearly intervals is a reasonable compromise with what is logistically possible. Clearly, extending the longitudinal study would provide further valuable information, particularly regarding staging DAT. The extension of SPECT imaging longitudinally would also yield useful information regarding the neural substrates for components of memory. Given the radiation exposure involved in SPECT imaging, retesting at somewhat longer than yearly intervals might be appropriate.

The tests employed have provided a suitable means of investigating most aspects of explicit memory although, with the benefit of hindsight, improvements are possible. For example, it is clear that executive function is very complex. Although we used two dual-performance tasks and letter fluency, these are almost certainly assessing some aspects of executive function. It may be that other tests of executive function would have correlated to a different extent with autobiographical memory,

and subsequently altered my conclusions regarding the role of executive function in the retrieval of autobiographical memories.

Anterograde episodic memory was assessed using three tests. Logical memory was used as it is part of the established Wechsler Memory Scale. The CERAD word list and the Doors and People Test are superior in that more insight is shed on the nature of the deficit underlying the episodic memory impairment. The Doors and People Test has been useful in studying recall and recognition, the forgetting rate, and verbal and visual memory. It appears to be a useful addition to the range of clinical tests of episodic memory.

Remote memory is necessarily more subjective than anterograde memory. With regard to famous person-based knowledge, the coadministration of the Famous Names Test with the Famous Faces Test led to a greater understanding of the deficit, in terms of current models of face and name processing. The use of a forced-choice paradigm for recognition, yet a free recall paradigm for identification and naming, was unfortunate. In future, presenting individual single faces or names as well as foils, with the instruction "Is this a famous person ?" would allow greater comparability between performance on recognition, identification and naming. By dint of the nature of remote memory, tests require updating to ensure that recently famous faces are included in the test.

The Autobiographical Memory Interview remains the only commercially available test of its kind. By altering the questions pertaining to the recent time period, it has been possible to obtain a better measure of recent remote memory. The original test, by enquiring about last hospital attended, is likely to be impinging on memory following the onset of the disease process. Although the autobiographical fluency test was devised to counter the problems in the AMI of ceiling effects in controls, I found that wide variability in controls' performance limited the use of the autobiographical fluency test.

The utility of SPECT in investigating DAT could be considerably improved. Technical and statistical advances now allow greater information to be derived from SPECT images. Manually drawing regions of interest onto SPECT images is an imprecise method of ascertaining regional cerebral blood flow. It is now possible to deform the SPECT images in the anterior-posterior or transverse axes in order to fit pre-defined templates. This leads to more accurate estimations of regional cerebral blood flow. Unfortunately, it was not possible to utilise this method of analysis with the SPECT data I collected. The use of activation studies rather than measuring regional cerebral blood flow would further enhance the power of SPECT.

Future investigations

Further insights into Alzheimer's disease, and brain-behaviour relationships in general, will be provided by longitudinal studies. The ideal means of investigation would be to study patients using detailed neuropsychology and imaging. Longitudinal studies of patients with initially minimal disease would be particularly useful. Ideally, such studies would continue until the patient was no longer able to comply with testing. Although clearly a sensitive issue, obtaining neuropathological evidence of the sites of maximal AD pathology at post-mortem would provide further invaluable information.

It is clear that DAT is a heterogeneous disease [38]. As mentioned previously, DAT does not always present with memory impairment, but may manifest initially with aphasia, agnosia, apraxia etc. Even within the majority of DAT patients who present with memory impairment, there is considerable individual variation with regard to the rate of cognitive deterioration, the order in which aspects of cognition (e.g. language, visuospatial and perceptual function) become impaired, etc. In order to deal with the amount of data in this thesis, I have compared the DAT patients as a group against controls, or have subdivided the DAT group into minimal and mild subgroups on the basis of the MMSE scores. The strength of longitudinal studies is that patterns of evolving cognitive deterioration in individual patients can be addressed. For instance, regarding minimal DAT patients with initially anterograde episodic memory impairment, some may subsequently develop working memory impairment, others may develop remote or semantic memory impairment, while others may continue to show an isolated anterograde episodic memory deficit. Collapsing patients' data into groups will mask individual heterogeneity. This problem could be circumvented by presenting individual longitudinal cognitive profiles for each patient. An alternative means would be to subject the longitudinal data to cluster analysis, which would select out subgroups of DAT patients with similar cognitive deterioration, e.g. combined episodic-working memory deficits, combined episodic-semantic deficits etc. It may be that certain cognitive profiles will be of use in prognosis, such as the controversial assertion that DAT patients who have early language impairment show a greater rate of deterioration [104].

Another area which could be developed relates to studies of remote memory. As discussed previously, remote memory is intrinsically difficult to test and subjective, given the difficulties of assumptions regarding premorbid knowledge and in checking the veracity of patients' autobiographical recollections. It is also difficult to place remote memory on the episodic-semantic spectrum. For instance, studies of remote memory often employ famous people tests. Recollection of some famous persons are episodic in nature, while others are more semantic. With respect to my Famous Faces Test, seeing a photograph of John Profumo is likely to activate

memories of London in the 1960s, Christine Keeler, and the Government scandal. Since then, Profumo has largely disappeared from public life. Thus, memory for John Profumo involves temporal and contextual cues, and is likely to be episodic in nature. Seeing a photograph of Groucho Marx, by contrast, is different. When one first becomes aware of Groucho Marx, e.g. seeing him in a film for the very first time, subsequent recollection of him may involve temporal and contextual cues (e.g. remembering the name of the film, the cinema). At this point, the memory of Groucho Marx will be episodic. In time, however, one will come across Groucho Marx many times in films and in newspapers, and knowledge of him will become more semantic in nature. It is thus difficult to be sure that equivalent memories are being sampled across the decades, and this makes interpretation of temporal gradients in particular problematic.

Study of the relationship between person-based semantics and general semantic memory is also beset by similar problems, being confounded by the time of acquisition of memories. Most general semantic memory is acquired in childhood, and is used repeatedly throughout life. Person-specific semantics, by contrast, will depend on when the public figure became famous. In addition, some famous people (e.g. John Profumo) are famous for a brief period, while others (e.g. Groucho Marx) are referred to regularly throughout life. The relationship between person-based and general semantics would be best studied by comparing items learned at the same time (e.g. childhood) and subsequently referred to similarly often (e.g. comparing general semantic memory with memory for public figures regularly referred to, such as Marilyn Monroe). By attempting to control for time of acquisition and frequency of recollection, it may be possible to more accurately assess whether person-based semantics and general semantics are truly distinct.

Similarly, the relationship of autobiographical memory and person-specific memory may be further addressed by matching as much as possible the nature of the memories being evoked. Thus, recollecting an incident occurring at school might be suitably compared with knowledge of a public figure who was famous in the subject's youth but then disappeared from public life. Similarly, knowledge acquired in early adult life and used subsequently on several occasions (e.g. one's National Insurance Number), might be more appropriately matched with knowledge of a public figure who came to prominence in the subject's early adulthood and remained in the public eye throughout the subject's adult life (e.g. the Queen). Autobiographical memory will, however, be more personally salient, and hence items must be matched for difficult. Such studies are clearly fraught with methodological problems, but are necessary to further delineate the nature of remote memory [142].

Advances in cognitive neuropsychology, both by group studies but particularly by detailed individual case studies, will further elucidate the internal architecture of memory. This in turn will lead to the development of more sophisticated neuropsychological instruments for measuring these components of memory. Hopefully, this will be complemented by the rapid advances in imaging, particular by activation studies utilising PET and functional MRI, which will lead to a greater understanding of the neural structures underpinning these memory components.

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Appendix

Patient information sheet - Memory impairment study

Please would you consider participating in our project which aims to study progression of memory impairment.

Disorders of memory affect up to 5 per cent of people over 65 years old and sometimes affect people below this age. There is a clear need for effective treatments for the condition.

A major goal is to develop treatments which slow down the progression of the illness. To be able to test such treatments, however, we need to know more about the natural course of the condition itself, and about which tests are most suitable for showing possible benefits.

In the current study a group of patients with memory impairment will be studied. Every year each patients will have a simple series of tests of memory, which will last about one hour. They will also be examined by a physician, and will have a SPECT scan, which shows how the blood flows to the brain. The SPECT scan does involve the use of radiation, but each scan is only the equivalent of other commonly used radiological procedures such as a barium meal. The tests and examination are commonly used in the clinic. Before entering the study each patient will have a routine medical check-up including blood tests and a CT brain scan (the scan will not be necessary if one has been performed within the last two years).

You are not obliged to take part in this study and may at any stage withdraw without needing to state your reasons. If you do not wish to participate or subsequently withdraw, it will not affect your treatment in any way.

All the information collected during the study will be kept completely confidential. The study doctors, Dr JR Hodges and Dr JDW Greene, will be available to answer any further questions, and are contactable on the following direct telephone number, Cambridge (01223) 217697 or 216739.

Yours sincerely,

John Greene
Research Registrar in Neurology to Dr Hodges

Famous faces and names used in Famous Faces and Famous Names Tests

1940s
Louis Mountbatten
Joseph Stalin
George Formby
Bing Crosby
Vera Lynn
Dwight Eisenhower
Clement Attlee
Aneurin Bevan
Groucho Marx
Lord Montgomery

1950s
Diana Dors
Richard Dimbleby
Grace Kelly
Harold MacMillan
Arthur Askey
Anthony Eden
Gilbert Harding
Rab Butler
Anthony Crossland
Pandit Nehru

1960s
John Profumo
Harold Wilson
Tony Hancock
Peter Sellers
Barbara Castle
Sid James
Hughie Green
Alec Douglas Home
Sean Connery
Sophia Loren

1970s
Michael Foot
Ayatollah Khomeini
Ian Botham
James Callaghan
Indira Gandhi
Jimmy Carter
Ken Livingstone
Elton John
Glenda Jackson
Michael Parkinson

1980s
Ronald Reagan
Esther Rantzen
Sarah Ferguson
Michael Heseltine
Arthur Scargill
Neil Kinnock
Steve Davis
Terry Wogan
Mikhail Gorbachev
Dame Edna Everage